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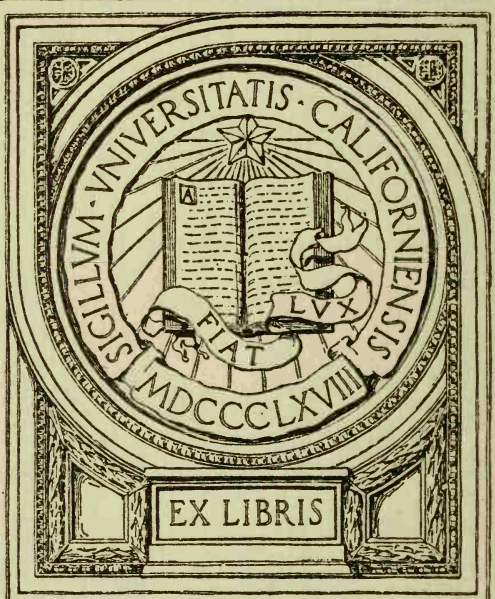

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LECTURES
ON
CHEMICAL PATHOLOGY

LECTURES

ON

CHEMICAL PATHOLOGY

IN ITS

RELATION TO PRACTICAL MEDICINE

DELIVERED AT

THE UNIVERSITY AND BELLEVUE MEDICAL SCHOOL

NEW YORK CITY

BY

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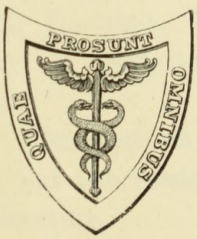

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PREFACE.

THE Lectures which make up this volume were delivered at the University and Bellevue Hospital Medical College during the Sessions of 1899–1900 and 1900–1901. I publish them in the hope that they will prove useful to students and practitioners of medicine who have not had the opportunity to keep in touch with modern research in the field of Chemical Pathology.

I have aimed only to sketch the leading characteristics of the physiological and pathological processes that have come under discussion, without describing these processes fully or systematically. It has been deemed best to omit some topics of importance which were presented in the Lectures, for example, the pathological chemistry of gall-stones and of fat necrosis of the pancreas.

The short list of references at the end of each Lecture is designed to put the reader on the track of the most significant literature.

C. A. HERTER.

819 MADISON AVENUE:
February 11, 1901.

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THE CHEMICAL DEFENCES OF THE ORGANISM AGAINST DISEASE

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Gentlemen,—I propose to discuss with you during the coming session some of the problems of chemical pathology, not so much from the standpoint of the chemist as from that of the practitioner of medicine. In consequence of the intense activity of numerous investigators, there are now a very large number of observations upon the changes in the chemistry of the human organism in disease, and in many instances it has been possible to gain some insight as to the nature of the processes that give rise to these changes. It will be my task to bring to your notice those

facts of chemical pathology which are most likely to be of service in the interpretation of the phenomena of disease, and hence most likely to aid you in the recognition and practical management of the derangements that present themselves in the course of medical practice.

During the coming winter our talks will relate especially to the chemical pathology of digestion, and I invite you to consider with me the following topics :—(1) The chief food-stuffs, and their fate in the body in health and disease; (2) the fermentative and putrefactive processes in the gastro-enteric tract; (3) the disorders of secretion and motility in the digestive tract; (4) the derangements of hepatic function ; (5) diabetes ; (6) starvation and obesity.

But before we enter on the discussion of these subjects I shall ask you to follow me in a sketch of the chief chemical defences of the organism against disease. It seems desirable to review our present knowledge of these defences, because it serves to emphasise the varied chemical activities of the cells in health, and to render more intelligible the phenomena of disease that result from the modification or failure of these cellular functions.

Modern pathology has made us familiar with the conception that disease is generally the expression of a reaction on the part of cells to injurious agencies. This general conception is fully borne out by everything that we know of the chemical reactions by which the individual defends itself against its organised enemies, the bacteria, and against the various poisons of bacterial and other origin. There are, indeed, modern biological observations which indicate that some chemical activities of a defensive sort can be carried on without the participation of the cell as a whole; or, in other words, that fragments of the cell body are capable of still carrying on functions after the cell has been subdivided by mechanical means. But the knowledge that fragments of protoplasm in the disintegrated cell are capable of exerting certain chemical activities does not in the least militate against the general applicability of the cell doctrine to the explanation of pathological processes. The only rational conception of the ability of the human body to defend itself against disease by means of chemical agencies is that these defences ultimately reside in the cells themselves. Many of the phenomena of disease are caused by the modification of function that occurs during the action of the cells in resist-

ing injurious influences. Let us consider the nature of this resistance in so far as it is accomplished through chemical agencies.

The chemical defences of the body are directed chiefly against bacteria, against bacterial toxins, and against poisons other than toxins formed during digestion, during metabolism, or introduced from without. Another important defence is that against bleeding, and depends on the coagulative property of the blood.

The acidity of certain fluids of the body constitutes a natural chemical defence, of a partial character, against the access of pathogenic organisms to the blood. Thus the acidity of the gastric juice in health is sufficient to destroy most of the bacteria introduced with the food, unless their number be very large or they are taken at a period of digestion when free hydrochloric acid is present only in small amount. Carefully conducted experiments indicate that the bactericidal action of the gastric juice on the spirilla of cholera is due chiefly to the free hydrochloric acid. But while it is likely that many of the micro-organisms of cholera are killed by the normal gastric juice, there is good reason to think that considerable numbers may pass unharmed into the intestine, even where free hydrochloric acid is present in the concentration in which it exists normally at the height of digestion. This is probably true, also, of the bacilli of typhoid fever. We are in need of more accurate information in regard to the bactericidal action of the gastric juice than we have at present. It would be especially interesting to know whether persons who secrete little or no free hydrochloric acid are more susceptible than others to infections arising through the digestive tract. In young children the gastric juice contains no free hydrochloric acid, and it is possible that this accounts in part for the susceptibility to digestive derangements which is observed during infancy.

The acidity of the urine is sufficient to check the growth of many species of bacteria, but has no influence on others. When the urine is only slightly acid or neutral the conditions are much more favourable for bacterial activity than if the urine is strongly acid. Whether the acidity of the sweat exerts any effect of a bactericidal nature is uncertain, but it is not unlikely that the volatile fatty acids which it contains are at least unfavourable to the multiplication of many species. In the case of the vaginal secretion, which

also has an acid reaction, due to lactic acid, the question of bactericidal action has been much discussed. It appears to me that the balance of evidence is distinctly in favour of the contention that the normal vaginal secretion either checks the growth of streptococci pathogenic to lower animals or diminishes their virulence. This action has been attributed to the lactic acid, but it should not be forgotten that the presence of bactericidal elements derived from the blood may play a part.

Far more important than any of these external and partial defences against bacteria is the bactericidal action of the blood and lymph. The bactericidal powers of the blood were discovered when the effort was first made to find in the blood a suitable medium for the growth of certain bacteria. It was found, contrary to expectation, that bacteria, even pathogenic bacteria, introduced into the blood serum not only failed to multiply, but were more or less energetically destroyed. An exception to this general bactericidal action relates to a few varieties of bacteria, which by repeated passage through animals have become so adapted that a very small number of individuals, possibly a single organism, would develop if introduced. This destructive action upon bacteria, which is one of the most important of the defences of the organism against disease, is gradually lost in from one to six months, even when the serum is kept sterile. The action is directed against all the ordinary pathogenic organisms, such as pyogenic streptococci and staphylococci, the tubercle bacillus, the typhoid bacillus, &c. The chemical character of the substances on which the bactericidal powers of the blood depend is not fully understood. The property seems due to the presence of proteids resembling the enzymes. The resemblance to the action of ferments consists, first, in the activity of the antibacterial substance in small amount; secondly, in not being destroyed by drying; and thirdly, in the destruction of the bactericidal property through exposure of the serum for one hour to a temperature of 55° C. There is, however, at least one important point of difference; for while the effect produced by the bactericidal substances appears strictly proportional to their quantity, the enzymes are seemingly able to cause changes without being necessarily used up or fixed in an inert compound. It is thought by some observers that the proteid substances which give to the serum its

bactericidal action are derived from the leucocytes. Hankin based this opinion on finding a relationship between the number of leucocytes in the blood and its bactericidal powers. The term 'alexines' has been applied to these substances.

There is another property of the blood serum which is very closely allied to its bactericidal action. This is the globulicidal action of the serum, by virtue of which the serum of an animal, injected into the circulation of a different species of animal, gives rise to a solution of the red blood corpuscles. This destruction of the red blood cells may be so considerable as to give rise to hæmoglobinuria. Both the globulicidal and bactericidal powers of the blood are destroyed by exposure to 55° C. for one hour.

The globulicidal substances of the normal serum are designated hæmolysines, whilst the bactericidal bodies are called bacteriolysines, these terms having their origin in the capacity of the serum to destroy foreign red blood cells and bacteria by bringing them in solution. These protective substances are also known as alexines. According to the original conception of Buchner, the alexine or protective substance in a particular species is present as a single substance. Recent experiments, ingeniously devised by Ehrlich and Morgenroth, seem, however, to show that the hæmolysines are complex bodies made up of two complementary substances, which, in turn, are resolvable into several closely allied but distinct substances. The presumption is that this is true also of the bacteriolysines. It is, perhaps, best to discard the term 'alexine,' as it conveys the erroneous idea that the substance is an entity.

The bactericidal power of the blood is by no means wholly due to properties belonging to the serum, but depends in part upon the leucocytes. Some observers attribute the bactericidal powers of the leucocytes to their phagocytic action, which enables them to incorporate and assimilate the bacteria by a sort of digestive process. Other students of the bactericidal powers of the leucocytes attribute this activity to alexines of a peculiar character in the body of the leucocytes. It is thought that the bactericidal action of the serum is dependent, at least in part, upon substances which are constantly escaping from the leucocytes into the serum. There is reason to think that the leucocyte contains bactericidal substances with different properties from those possessed by the globulicidal materials of the serum. Thus

one observer found that the bactericidal action of the leucocytes does not depend on the presence of the salts of the blood serum. The bactericidal action of the serum, however, is very largely or completely lost when the salts are dialysed away. Then, again, it was found that the bactericidal material from the leucocytes has not the power of dissolving the red blood cells of alien species of animals. This, you see, constitutes an important point of difference from the bactericidal substances of the serum, which appear to be closely bound up with the globulicidal action of the blood. It is not quite clear, however, that the same substance is actually responsible for both the globulicidal and bactericidal activities of the serum; in other words, that the hæmolytic and bacteriolytic substances are identical. I think there is no doubt that the bactericidal powers of the leucocytes have been considerably exaggerated by some investigators. There is a growing inclination among pathologists to believe that the leucocytes attack only such bacteria as have been already killed or somewhat injured by the action of bactericidal chemical substances in the blood. To these substances the leucocytes contribute their share, as I have already explained, but this share is probably less important than the combined action of all the other cells of the body.

The bactericidal action of the blood as a whole is a remarkably persistent property. Even conditions which greatly reduce the strength of an animal do not destroy the general bactericidal action of the blood. Thus it has been found in dogs that after five days' fasting the action of the blood as a whole and of the serum against typhoid bacilli was not diminished, but it is true that both the general bactericidal power and the specific action in particular species are often lessened in states of disease.

The bactericidal action of the blood is closely connected with its alkaline reaction. This reaction depends on the presence in the blood of carbonates and phosphates, especially those of sodium. The alkali of the blood is present in two forms, partly in combination with albuminous materials, as albuminates, and partly in solution in the serum. If a current of CO_2 be passed through the blood it displaces a portion of the albuminates, especially in the red cells, where this combination of alkali and albumin is most abundant. The result is that the newly formed carbonate diffuses into the serum and renders it more alkaline. An

increase in alkalinity of the serum outside the body through the addition of carbonic acid gives rise to a distinct increase in the bactericidal power of the serum. Thus it is stated that the serum from the jugular vein may contain as much as 25 per cent. more diffusible alkali than the serum from the carotid blood, and possesses correspondingly greater bactericidal action. This fact is of much practical interest in the consideration of the chemical defences against bacteria, and it is a fact which has already been employed with some success in the treatment of disease. Surgeons have learned, in treating tuberculosis of joints, that the tuberculous process is rendered less active through the action of venous stasis at the affected point. It seems probable that such benefit as has been obtained from the use of this method is due to the increase of bactericidal action of the lymph, more than to that of the blood. It has been observed that in the case of inflammatory œdema the bactericidal power of the lymph is greater than that of the blood serum. This is the reverse of normal conditions. The bactericidal action of œdema lymph is also much greater than that of normal lymph, and this difference seems to be attributable, at least in part, to the greater content of alkali.

Whether the increased alkalinity of the serum contributes to the bactericidal action of the blood through its direct effect, or through its favourable influence upon the oxidative powers of cells, is uncertain. It is, however, quite clear that those oxidative processes in cells which are so closely connected with the maintenance of life are distinctly favoured by the normal alkalescence of the blood, and are hindered when this is diminished. A considerable reduction in the alkalinity of the blood for a prolonged period is incompatible with the maintenance of life. Considerable fluctuation in alkalescence probably occurs in many cases of disease, but the conditions under which the variations from health occur are not fully understood. I think we may say that in states associated with diminished alkalescence of the blood, such as chronic nephritis and diabetes, the susceptibility to infections is markedly increased, but it is not certain that this depends on the diminished bactericidal power of the serum. So far as the bactericidal action of the serum is concerned, we may conclude that this property is really independent of the alkalescence of the blood, though it may be greatly modified by it. Furthermore, it seems likely that

the bacteriolysines are derived from the cellular elements of the organism, and especially from the leucocytes. We have no definite knowledge of the chemical nature of the bacteriolysines. There is some confusion as to the clinical states in which the alkalescence in the blood is positively diminished. This is owing in part to the practical difficulties attending a satisfactory estimation of the alkalinity of the blood. It is clear, however, that in diabetic coma there is regularly a distinct diminution in alkalescence, and the same is true of some cases of nephritis. Moreover, there is satisfactory evidence that the coma of diabetes depends on this reduced alkalescence of the blood. In this particular instance the reduced alkalescence is referable to the presence of a form of oxybutyric acid. The fact that stupor and coma may depend on an acid intoxication has been experimentally demonstrated. The diminished alkalescence of the blood in anæmias appears to be due to a reduction in the blood proteids and in the alkali which belongs with them.

Quite distinct from the bactericidal and globulicidal properties of the blood is its agglutinating action. You are doubtless aware that as the result of infection with many kinds of bacteria, or of the introduction of their toxins, the blood develops the remarkable property of immobilising and clumping together the specific organisms on which the infection or intoxication depends. It is believed that these remarkable phenomena, so well displayed in the reaction of the blood of typhoid fever, known as Widal's reaction, depend on the presence of a proteid substance, for it is precipitated from blood plasma with fibrinogen and globulin. It also behaves like a proteid in respect to filtration and dialysis.

The agglutinative property is more resistent to injurious agencies than the bactericidal property. The agglutinative action is lessened by prolonged heating at 60° C., but is not destroyed unless subjected to a higher temperature.

It is important for you to recognise that the specific bacteriolytic and agglutinative substances have never been isolated as chemical compounds. This is true also of the antitoxic substances. Indeed, the view has been expressed by Behring that the isolation of pure antitoxin is hopeless, since in his opinion it is a force pertaining to highly organised material rather than a substance, and is no more likely to be isolated than the magnetic force from an iron

magnet. This idea of the nature of the antitoxin has been applied also to the agglutinative and bactericidal properties of the blood. Attractive as is this hypothesis, I do not think we should commit ourselves to it at present, for there are some recent observations which speak rather in favour of a material separable antitoxic substance than for the idea that the antitoxic property depends on a peculiar physical state of proteid substance.

The most reasonable view of the agglutinative property seems to me that of Bordet, who contends that there is an agglutinating agent ('agglutinine') which acts upon an agglutinable substance ('substance agglutinée'), and that the reaction occurs not alone with bacteria but in dead material, such as dead bacteria, casein, and various precipitates.

There is no reason to believe that the agglutinating property is in any way connected with the flagella of bacteria. Neither have we sufficient reason to believe that agglutination is a specific property connected with a state of immunity. There is no definite relation between this property and the bactericidal action of the serum. Moreover, we have to relinquish the idea that agglutination in infectious diseases is a phenomenon of a strictly homologous nature, since it is true, for example, that typhoid bacilli are clumped by diphtheria antitoxin as well as by typhoid serum.

From what has been said it must be plain that the origin of the agglutinating power of the blood is still obscure. The property is doubtless given the blood as the result of cell activities, and probably, as in the case of the bacteriolytic powers, through the passage of certain substances from the cells of the body, including the leucocytes, into the blood.

The antitoxic action of the organism—that is, the ability of the body to produce a substance or substances capable under certain conditions of neutralising the injurious action of bacterial toxins—is certainly one of the most remarkable chemical defences of the animal body against disease. Some animals produce antitoxic substances naturally, others only under certain special conditions. It is impossible here to enter into a full discussion of the nature of the antitoxic defences of the body. Certain features of this defence may, however, be briefly reviewed. It is now well known that an animal inoculated with pathogenic bacteria, or poisoned with the products of such bacteria, is capable of developing in time an immunity against the harmful action of the

same bacteria or their toxins. This immunity consists in the ability of the organism to destroy pathogenic bacteria through the bacteriolytic action of the blood, or to neutralise the products of these bacteria. These two actions, the antitoxic and the bacteriolytic, though frequently associated, may be entirely distinct. Thus Wassermann, on studying the action of the bacillus pyocyaneus, found that the immunity produced by the injection of the pyocyaneus toxin was both antitoxic and antibacterial, that is, capable of protecting the immunised animal against both the bacterial poisons and the bacilli themselves. On the other hand, the immunity induced by the bacilli alone was only antibacterial, and did not suffice to protect against the products of these organisms.

The injection of the living bacteria of many species is followed by the production of an almost exclusively bactericidal serum, while the injection of such highly specific toxins as those of diphtheria or tetanus leads to the production of an almost exclusively antitoxic serum.

Immunity induced by the development of protective substances in the body is usually called active immunity, whereas that produced by the injection of protective sera is spoken of as passive immunity. The active immunity is more lasting than passive immunity. One reason for this appears to be that protective substances formed in the body of an animal, or introduced into one of its own species, are longer retained than when these substances have been formed in the body of an animal of another species.

Much careful study has been devoted to determining the nature of the antitoxic action of the blood and tissues, and although many of the facts connected with the establishment of immunity are still unexplained, it has been possible to formulate an hypothesis which accounts for very many of the observed facts. The theory of Ehrlich as to the nature of immunity is the most ingenious and far-reaching hypothesis that has yet been proposed.[1] This theory rests on

[1] Since the preparation of this lecture Ehrlich has modified and developed his side-chain theory of immunity. He emphasises the fact that toxins (which resemble proteids and proteid derivatives in their chemical constitution and origin) are capable of uniting with the protoplasm of living cells in virtue of the possession of groups like those by which the nutritive proteids become united to cells in the course of normal assimilation. The term 'haptophore group' is applied to the group of atoms by which either the toxin molecule or the nutritive pro-

certain fundamental propositions that are well supported by facts. In the first place it is clear that the toxins which call forth the production of antitoxic substances in disease are not actually destroyed, but rather are neutralised, by the antitoxic bodies. This has been very clearly demonstrated in the experiment of Calmette with snake toxin and antitoxin. In diphtheria and tetanus the antitoxin is more resistent to the action of heat than the toxin itself, but in the case of snake poison the conditions are just reversed. That is to say, the antitoxin is destroyed at a lower temperature than that which destroys the toxin. Thus, upon mixing the toxin of poisonous snakes with the corresponding antitoxin, so that the mixture became entirely harmless to the animals experimented on, it was found that on the application of a temperature of 68° C. the toxic properties of the mixture reappeared just as strongly as though no antitoxin had been added. Similar results have been obtained in the study of the toxins and antitoxins of the bacillus pyocyaneus. Such results as these are quite inexplicable on the supposition that the toxin has been actually destroyed.

The next proposition essential to the establishment of Ehrlich's hypothesis is that the action of the antitoxin on the toxin is of a purely chemical nature. In the case of the poison ricin and the antitoxic body antiricin, produced by its action, it has been shown that the quantity of antiricin necessary to neutralise a given quantity of ricin is exactly the same in the body itself, and in test-tube experiments in which there is no possibility of the cells taking part. These results on ricin have been duplicated in experiments upon snake poison, upon the poison of tetanus, and upon diphtheria toxin. They make it clear that a mere

teid molecule becomes attached to the receiving groups or 'receptors' of the cells. The resemblance between the physiological assimilation of proteid and the union of cell receptors with toxins is illustrated by the fact that both nutritive proteids and toxins are capable of inducing the formation of 'anti-bodies' which stand in a specific relation to the stimulating agent. Thus milk and various sera (*i.e.* nutritive non-toxic substances) introduced into animals cause the production of substances capable of coagulating the proteids introduced by entering into chemical union with them. According to Ehrlich, the introduction of a toxin is followed by an excessive production of receptors, which are finally thrown off into the circulation as unused ballast. The free circulating receptors are the antitoxin (see Ehrlich's 'Schlussbetrachtungen,' in Nothnagel's *Specielle Pathologie und Therapie*, Bd. viii., 1. Theil, iii. Heft, s. 163, 1901).

chemical union of the toxin with the antitoxin within the body is all that is necessary to render the toxin harmless. Examples of a similar character are well known to chemistry. Thus the extremely poisonous properties of cyanide of potassium are destroyed by a combination with cobalt, and carbolic acid loses its toxic action through combination with sulphuric acid.

It is, of course, well known that the production of an antitoxic substance is not induced by all poisons. It is, therefore, clear that those bodies which are capable of exciting the formation of an antitoxin must possess some peculiarities other than the property of inflicting chemical injuries on cells. According to Ehrlich's view this peculiarity consists in the fact that a body capable of inducing antitoxin formation possesses a chemical affinity towards certain constituents of the cell which have been designated the 'side-chain.' This word 'side-chain' has no histological significance, but rather a purely chemical one. It is a side-chain in the sense in which this term is employed in speaking of chemical compounds which, in addition to the principal or central group of atoms in the molecule, possess one or more lateral groups of atoms, which are more readily attacked or replaced than any other atoms in the molecule. Every chemist is familiar with the remarkable changes in the properties of bodies which take place through introducing new groups into such side-chains. Nevertheless, the introduction of these groups may not alter the character of the central group of atoms which constitute the chemical nucleus of the compound. As simple examples we may point to the introduction of the NH_2 radical into the benzol ring giving rise to anilin, or the introduction of the group OH giving rise to phenol. Similarly, we may imagine that the complex molecules of the protoplasm of cells are provided with various groups of atoms constituting the side-chain. Now, according to the side-chain theory of antitoxin immunity, the toxin which enters the blood is carried to certain cells, where, owing to the existence of special chemical affinities, a union occurs between the toxin and certain side-chains of the protoplasmic molecule. The cells of the body thus tie up the toxin. But the toxin thus tied may act injuriously on central groups of the protoplasmic molecules, and in this way interfere with vital processes. It is this injurious action which gives rise to modifications in the functions of

the cells of the body in the course of toxin poisonings, and is also capable of giving rise to histological changes. The union of certain vulnerable side-chains to molecules of the toxin may, however, be consistent with the carrying on of normal processes in the cell. As the result of such processes there is a regeneration of side-chains similar to those which have become united to the toxin. In fact, the injury inflicted on the cell through the action of the toxin (if not excessive) stimulates the cell to the production of side-chain groups in abundance, and certain of these become detached from the cell and enter the circulation. These protoplasmic groups which are thrown off through the blood under the influence of the stimulus afforded by the toxin are nothing less than the antitoxin itself. The process of antitoxin formation, according to this conception, is thus simply an exaggeration of a normal cellular activity in the course of which certain constituents of the cell pass over into the blood.

The same substance, or rather the same peculiarity, in the chemical composition of the living cell which constitutes the vulnerable element in poisoning by toxin becomes the cause of a curative action when it enters the blood. The side-chains are not to be regarded as exerting an antitoxic action while attached to the living cell, but only when they become a part of the blood. It seems likely that, although the side-chains of the cell substance neutralise the toxin just as effectively as when they are free in the blood, they can hardly be regarded as effectively antitoxic, because in the act of neutralising the toxin the cells suffer injury.

The Ehrlich hypothesis has been subjected to various experimental tests by different investigators. Thus Wassermann reasoned that if the antitoxic substance be really a constituent and product of the normal cell, though formed in excess, its presence should be demonstrable in the normal cells. The tetanus toxin acts especially on the nervous system, and one would expect that some evidence of antitoxic powers should be exhibited by the structures, or rather substances, which make up the central nervous system. Such an action was, in fact, found to exist. An emulsion of the brain of a normal guinea-pig injected into a normal animal, together with tetanus toxin, enabled the animal to withstand ten times the fatal dose of the toxin. Other tissues than those of the nervous system gave negative results. These observations have been confirmed by other

investigators. It has further been found that if a pigeon be killed with tetanus toxin the nervous system of this animal possesses no toxic properties, whereas indications of the presence of the toxin in other tissues can be obtained. This fact constitutes further evidence that the toxin is neutralised in the central nervous system. The side-chain hypothesis of antitoxin immunity has met with strong opposition from certain investigators, and its validity is still a question which is actively discussed. Roux and Borrel, for example, made the interesting observation that a different type of experimental tetanus can be induced in rabbits by introducing the toxin directly into the brain, instead of giving it subcutaneously. It was found that the quantities required to kill are very much less than when the subcutaneous mode of administration is employed. Roux and Borrel consider that if the antitoxin were really produced in the brain, in accordance with the views of Ehrlich and Wassermann, it should be capable of neutralising the toxin as well when applied directly to the brain as when injected subcutaneously. But it is only fair to point out, as Weigert has done, that this criticism rests on a misconception of the side-chain hypothesis. According to this theory, the brain does not contain a protective substance ready-made against the tetanus toxin, but only produces it as the result of injury to the nerve cells. It must also be admitted that the direct application of the toxin to the brain brings the poison into contact with the nerve cells in much more concentrated form than when it is introduced subcutaneously. This difference in the mode of application of the toxin is so great that it is hardly fair to make comparisons of the two methods, in the expectation that they will yield the same results.

Other objections to Ehrlich's side-chain theory have been raised by the Metschnikoff school of investigators, who contend against a purely chemical explanation of antitoxin immunity. In their view this immunity is due to biological processes, in which the leucocytes play a principal part, a part in some way bound up with the phagocytic action of the leucocytes. Thus Metschnikoff emphasises the fact that the exudate which follows the injection of bicarbonate of soda into the peritoneum in an animal actively immunised possesses a stronger antitoxic action than the blood itself, and also contains many more leucocytes than the blood. To this it may be said that the stronger antitoxic power of

the exudate can scarcely be referable to the rich content of leucocytes, since it is possible to induce an exudate in other parts of the body, in the same animal, which possesses a very weak antitoxic power, notwithstanding the presence of large numbers of leucocytes. Nevertheless, it cannot be denied that the leucocytes play a part in the production of some form of antitoxic immunity, though by no means an exclusive one. The difficulty is to definitely determine their *rôle*.

The objection to the side-chain theory has also been raised that it fails to explain the circumstance that diphtheria toxin, neutralised outside the body by means of antitoxin, continues to stimulate the production of antitoxin when injected into the body. But if it be true, as already stated, that the toxin and the antitoxin enter into a chemical union which does not actually destroy the chemical structure of the toxin, it is conceivable that the poisonous action of the toxin may be greatly modified without depriving the neutralised toxin of the power to stimulate the production of antitoxic side-chains.

It is a significant fact that specific antitoxic substances are normally present in the blood of certain animals. Thus Bolton, Park, Atkinson, and others have found that more or less of the antitoxin of diphtheria is present in the blood of all horses. In some the amount is small, but in others it is equivalent to three antitoxic units to each cubic centimeter of the serum. Now we can hardly assume that diphtheria bacilli have induced antitoxic production in all horses. It is more reasonable to suppose that the antitoxic substance is normally formed by the cells of the horse, and thrown out into the serum without any introduction of diphtheria toxin.

On the whole, it seems more likely that the antitoxic and protective substance is formed as the result of stimuli to normal cells rather than to an actual injury of cells. The nature of the stimulus that results in the formation of diphtheria antitoxin in normal horses is quite unknown to us.

It is to be remembered, in any consideration of immunity, that unless the cells of an animal contain substances capable of being injured by toxins, the introduction of such toxins is not followed by the development of symptoms; the same toxins brought in contact with other cells, provided with vulnerable substances,[1] are no longer inert and

[1] Ehrlich's 'receptors.'

harmless. We have here the explanation of the natural immunity of some animals to powerful toxins, examples of which are the exemption of the grey rat to diphtheria toxin, and the immunity of the hen to tetanus. It seems probable that the amount of sensitive substance in the cells of any animal influences distinctly its susceptibility or immunity to bacterial poisons.

The interesting observation, recently reported by Park and Atkinson, that in diphtheria there is a close connection between the globulin of the blood and the antitoxic strength, harmonises with the side-chain hypothesis in so far as it indicates that the antitoxic substance is the product of general cell activity. Modern physiological studies teach us to regard the globulins of the blood as arising from the activities of several different kinds of body cells. Now Atkinson finds that the stronger the antitoxin production in horses the greater is the percentage of globulins in the serum. If all the globulins be precipitated, all, or nearly all, of the antitoxin is thrown out at the same time. When the different globulins are thrown out at different temperatures, portions of the antitoxin go down at each precipitation with the globulin. While it is by no means clear that the antitoxin is a globulin, the proportionate increase of globulin and antitoxin suggests this possibility in the case of the diphtheria antitoxin.

Recent studies by Pawlowski indicate that in immunised animals the different organs and different kinds of cells are very unlike in the amount of protective substances which they contain. Thus in guinea-pigs the bone marrow and the spleen were found to have most influence against the staphyloccus pyogenes aureus, whereas the cells of the liver and brain had little effect. These inequalities in the protective action of different cells help us to explain the distribution of bacteria in disease. In the case of non-immunised animals, even greater inequalities in the distribution of protective substances are observed.

The side-chain explanation of antitoxic immunity is, after all, only a highly ingenious hypothesis, well worthy of consideration. One reason why I have dwelt on it here is that it gives us an excellent vantage-ground from which to review many of the prominent facts of antitoxic immunity.

You are, of course, aware that in recent years much

attention has been devoted to the subject of serum therapy, and that a considerable degree of therapeutic success has been achieved in the human subject through the use of antitoxic sera. The use of the anti-diphtheritic serum is now firmly established. The serum of tetanus is only preventive and not usually curative, very likely owing to the fact that the antitoxin, as ordinarily introduced, does not combine with the toxin, because of the previous union of the toxin with the protoplasm of the nerve cells. The Calmette serum against snake-poison is apparently also an antitoxic serum. Other sera have been tried without therapeutic success. This is true of those against cholera, the streptococcus, the pneumococcus, the bacilli of typhoid, and other organisms. These sera are capable, to some extent, of killing the bacteria in question and of dissolving them; but they do not effectually destroy the bacteria in septic states, nor do they neutralise the poisons which the bacteria produce, and are of little or no curative value. They are bactericidal to some extent, but not antitoxic.

Ehrlich and Wassermann have recently offered an ingenious explanation of the failure of these sera to exert a therapeutic action. I have already mentioned that Ehrlich's experiments indicate that the bactericidal and globulicidal properties of the serum are dependent on more complex conditions than has been hitherto supposed. According to his most recent view at least two different bodies are necessary to render a serum bactericidal. One is the *inter-body* or *immunising body*, the other is what he calls the *end-body* or *complement* (formerly called addiment). The presence of at least two distinct substances in hæmolytic serum is shown by the following considerations. The repeated injection of red blood-cells of one animal (*e.g.* goat) into the blood of an animal of another species (*e.g.* sheep) after a time renders the latter animal immune to further injections, and at the same time causes the production of a serum which dissolves readily the red blood-cells of the first animal. The hæmolytic property of the serum is destroyed by heating to 56° C. for half an hour, but returns when fresh serum from the first animal (goat) is added. The specific immunising substance formed in the sheep is called the *immune-body*. The ferment-like body which is destroyed by heat is the *complement*. The latter is not specific, since it is furnished by the blood of animals which have not been immunised,

but it is essential to the formation of a hæmolytic serum. The immune-body is believed by Ehrlich to have two haptophore groups, one which connects with the receptor of the red cells, and one which unites with the haptophore group of the complement, and thus makes possible the action of the ferment-like complement on the red cells. Similarly, in the case of bactericidal sera, there are two substances necessary to the solution of the bacteria, an immune-body which fixes the bacterial receptors, and links the bacteria to the complement, which then exerts its destructive action on the micro-organisms. The *end-body* is a sort of digestive ferment which is capable of dissolving bacteria. It is present in normal serum, but can act only when it is bound to the bacterial cell by means of the immunising body. While the end-body is present in normal serum the immunising body is present only in amounts too small to be effective. The various anti-bacterial sera which have proved therapeutic failures are rich in the immunising body, but probably too poor in the ferment-like end-body. It seems reasonable to believe that by increasing sufficiently the quantity of the end-body many sera may become therapeutically efficient in the human subject.

Wassermann has already obtained highly interesting results in animals by working on the hypothesis just described. By adding the fresh serum of normal animals to the anti-bacterial typhoid serum containing an abundance of the immunising body, he succeeded in keeping alive guinea-pigs so infected with typhoid bacilli as invariably to die when treated with the almost useless immunising serum only. This result is attributed to the large quantity of the end-body contained in the normal serum. We cannot foresee to what therapeutic results the experiments conducted on these lines may lead. I strongly recommend you to read the papers of Ehrlich and Morgenroth on hæmolysines, as they open up an entirely new field of study.[1]

[1] Since the publication of the papers given in the list of references these writers have made other important contributions to the subject of hæmolytic sera (see *Berl. klin. Wochenschr.*, Nos. 21 and 31, 1900; No. 10, 1901). This work upon hæmolysines is important because it gives us a new method of studying the biological characters of the blood, and because the conditions which lead to the formation of hæmolytic sera closely resemble the conditions for the production of bacteriolytic sera. We may confidently expect important therapeutic methods to arise from studies pursued along the lines opened by Ehrlich and Morgenroth.

It is instructive to consider some of the chemical defences of the organism against poisons other than toxins. Many of these bodies are formed during the process of normal digestion, and some of them are apt to be formed in more than usual amount during certain disturbances of digestion. Thus acetic and lactic acids, derived from carbohydrate food, and phenol and indol, formed from the putrefactive cleavage of proteids in the digestive tract, may be produced in considerable amounts in pathological states. Other examples of digestive products, with somewhat poisonous properties, are the albumoses and peptones, which occasion characteristic disturbances when introduced directly into the circulation. Another class of toxic substances which deserve attention are those produced in the course of metabolism—*e.g.* ammonia and certain oxy-acids, including β-oxybutyric acid. Various internal secretions of glandular organs are capable, when formed in excess or when imperfectly neutralised or imperfectly utilised in the organism, of giving rise to toxic symptoms. The failure of certain internal secretions to be produced in sufficient amount may also be the occasion of marked disturbances in nutrition. This is the case with defective secretion from the thyroid gland, which results in the excessive accumulation of mucin in the blood and certain tissues. Still a third class of poisons is to be considered. These are poisonous substances introduced from without, for the most part by way of the mouth. An example of such a poison is alcohol.

Prominent among the chemical defences which operate against poisonous action of substances belonging to the group which I have just mentioned are the oxidative processes and the decompositions which attend these processes of oxidation. Secondly, these defences include certain processes of hydration and dehydration which are of common occurrence in the organism. Thirdly, they include various syntheses which possess a very considerable importance in bringing about detoxication within the body. We will consider in turn some of the leading features of these different types of chemical defence.

Taking first the oxidative processes which go on in the body, together with certain highly important decompositions, we are impressed at the outset with the wide distribution of such processes. The capacity to carry on processes of oxidation at the normal temperature of the human body is

one of the most remarkable and fundamental of all cellular activities. Even at the present day it is by no means clear how it is that the cells of the body are able to take from the red blood cells a supply of common or neutral oxygen, and by means of this oxygen to carry on a highly active process of combustion, a process through which the various complex molecules derived from the different food-stuffs are broken down into simpler substances with a yield of living energy. We know very well, for example, that, no matter how intimately the ordinary oxygen of the air is brought in contact with fat at the body temperature, there is no combustion whatever. Yet fat is easily burned by means of oxidation carried on in the cells.

Several views exist as to the nature of the normal oxidative process. According to one of these views, oxidation occurs in consequence of a splitting in the oxygen molecules, which causes a separation of two atoms of active oxygen. The separation of the oxygen molecule into atomic oxygen gives it the characters of the nascent gas, and thus permits the energetic action upon oxidisable materials in the cell. In this theory it is not quite clear what occasions the splitting of the molecules of oxygen. According to a view which was strongly advocated by the distinguished investigator Hoppe-Seyler, the oxygen atom is set free by the action of nascent hydrogen, which is formed in the course of certain decompositions—for example, in butyric acid fermentation. It is assumed that a somewhat similar decomposition with the liberation of hydrogen takes place in the cell, and that this is the cause of a split in the oxygen molecule.

It is probable that the presence of iron in the nucleoproteids of the cells plays an important part in giving oxygen to the cell itself. As is well known, oxides of iron exist in two forms—a ferrous form, in which there is a smaller proportion of oxygen, and a ferric form, in which there is a larger proportion. It is well established that the ferric compound is easily reduced to the ferrous state, and again easily oxidised to the ferric state. Assuming that iron exists in the protoplasm of cells in different degrees of oxidation, it is easy to see how iron comparable to that in the ferrous state would readily take up oxygen from the blood and be changed to the ferric state, only to be immediately reduced again to the ferrous state by yielding the new atom of oxygen to the cell itself. In this way we may imagine

that there is a continuous series of reductions and oxidations in the iron compound by means of which the oxygen of the blood is transferred to the cell. This oxygen, loosely held by the cell, is utilised by the cell-substances in effecting oxidations in food material which it is engaged in appropriating. That the cells of the body generally are capable of bringing about oxidative changes can be demonstrated even in the case of cells that have been removed from the body. If the cells of any parenchymatous organ, finely divided into a pulp, be brought in contact with easily oxidised substances, such as formic or acetic aldehyde, these compounds are readily oxidised to the corresponding acids, formic and acetic. Similarly, benzoic aldehyde is oxidised to benzoic acid, and arsenious to arsenic acid. It is a peculiarity of all these oxidations that they are easily brought about. In fact, they occur to some extent, and slowly, on exposure of these substances to the air. The oxidations which go on in the cell are, in part, of this simple character; but there are others of a very different kind. For example, the oxidation of the sugars involves a degree of oxidative energy very much greater than that which is exhibited by the cells outside the body. The conditions which enter into these more difficult oxidations are only imperfectly understood. It is assumed by some students that the presence of a special enzyme or ferment is an essential condition in the oxidation of substances like sugars and fats, and is also essential to the disruption of their molecules into simpler substances. In the case of sugar there is, indeed, some evidence that the splitting and oxidation of the carbohydrate molecules occur under the influence of a ferment-like substance furnished to the organism by the pancreas. It is not quite clear whether the oxidation precedes the decomposition or splitting of the molecule or follows it.

I have indicated to you that the presence of iron in the cells is essential to the oxidations which they carry on. A condition equally necessary to these processes is the maintenance of an alkaline reaction in the fluids which bathe the surface and permeate the interior of the cell. The requisite alkalescence is furnished by the alkaline carbonates and phosphates of the blood. Now please observe that this alkalescence is ultimately referable to the presence of hydroxyl (OH) ions in the blood and lymph. Thus sodium carbonate (Na_2CO_3) in the presence of the water of the

blood may be regarded as existing in the blood as the hypothetical carbonic acid (H_2CO_3) and sodium hydroxide (NaOH). The equation shows this relation :—

$$Na_2CO_3 + 2H_2O = H_2CO_3 + 2NaOH.$$

The hypothetical carbonic acid undergoes dissociation to only a limited extent. On the other hand, the sodium hydroxide is readily dissociated (see Lecture IV.) into its positive and negative ions, thus :—

$$Na^{+} \; Z \; OH^{-}.$$

We are as yet entirely ignorant of the way in which the hydroxyl ions play their part in aiding oxidation, and are in the field of speculation when we undertake to offer an explanation. It is conceivable that these ions act directly in the oxidation of protoplasm, either by the replacement of hydrogen atoms or by a liberation of (nascent) oxygen simultaneous with the formation of water. But it is also possible that these ions act indirectly through the ability of hydroxides to dissolve the carbon dioxide constantly formed by the cell, and thus at the same time free the cell from something which mechanically interferes with the appropriation of oxygen and afford a condition favourable to the transportation of the carbon dioxide to the lungs.

I wish now to give you a few examples of oxidative changes which protect the organism against the action of poisons. We may take first the oxidation of indol. Indol is an aromatic substance formed in the course of the digestion and putrefaction of proteids in the intestine. In some pathological conditions it is formed in large excess. It possesses distinct, though not very marked, toxic properties. Indol is absorbed as such from the intestinal contents, and enters the body. Somewhere in the body, perhaps especially in the cells of the liver, indol is oxidised to indoxyl. This oxidation is apparently an essential step to the union of the radical indoxyl with sulphuric acid. This union or synthesis occurs largely in the liver cells. As a result there is formed a new substance, the indoxyl sulphate of potassium. This new body is much less toxic than indol, and is readily eliminated by the urine. In this case the process of oxidation merely constitutes a link, although an essential link, in the process of detoxication. Another example of the detoxi-

cating action of oxidative processes is seen in the case of acetic acid, which is often formed in excessive amount in the course of fermentation of carbohydrates. Acetic acid possesses only slight toxic properties in the quantity in which it is ordinarily absorbed, even in pathological conditions. But it may have deleterious effects when continuously introduced even in small amounts, although the nature of these effects is not fully understood. In the body the oxidation of acetic acid leads first to formation of formic acid, carbonic acid, and water. The carbonic acid is eliminated by the lungs or utilised in the body. The formic acid, through still further oxidation, breaks down into carbonic acid and water. These various changes are indicated by the following equations:—

Acetic acid: $CH_3COOH + O_3 = H.COOH + CO_2 + H_2O$.

Formic acid: $H.COOH + O = H_2O + CO_2$.

Still another example is the oxidation of ethyl alcohol in the body. The human organism in health is capable of burning a certain quantity of alcohol into carbonic acid and water after first producing ethyl aldehyde and acetic acid.

Ethyl alcohol: $C_2H_5.OH + O$
$= \text{ethyl aldehyde } CH_3.CHO + H_2O$.
Ethyl aldehyde: $CH_3.CHO + O = CH_3COOH$.

There can be little doubt that this destruction of the alcohol molecules operates to protect the cells against injury at the same time that the alcohol is utilised as a food-stuff.

There are many other examples of the detoxicating effects of oxidation upon harmful chemical agents.

Whether processes of oxidation play a rôle in the development of antitoxic substances under the stimulus of bacterial toxins is a question which cannot be answered at present.

Processes of reduction, that is, chemical processes involving the removal of oxygen from compounds containing this element, are as prominently concerned as oxidations in the physiological activities of the cells. Indeed, these reductions are the necessary accompaniments of oxidations, the two occurrences, oxidation and reduction, standing in a reciprocal relation to each other. The formation of reducing substances in fermentation and putrefaction is well

known. We know, for example, that when sugar undergoes butyric acid fermentation there is a liberation of free hydrogen, thus :—

$$C_6H_{12}O_6 = C_4H_8O_2 + 2CO_2 + 2(H_2).$$

Now we assume that when easily oxidisable bodies like hydrogen are produced during fermentation the oxygen molecule (O_2) is split into its atomic state, one atom of oxygen uniting with two of hydrogen to form water, while the remaining oxygen atom is liberated with the oxidising properties of the nascent gas.

In the animal organism easily oxidisable substances, that is, reducing substances, are constantly being produced by the cells. This is evident from the fact, first observed by Ehrlich, that alizarine blue, indophenol blue, and other colouring matters lose their colour while in the cells and fluids of the body by parting with their oxygen to regain their colour on exposure to air. It is evident also from the observations of Ludwig and Alex. Schmidt that readily oxidisable reducing substances accumulate in the blood of animals deprived of oxygen.

We are ignorant of the conditions that determine the production of these reducing substances from protoplasm. There is some reason to believe that unorganised ferments or enzymes are essential to some of the cleavages of protoplasm and, perhaps, also to the oxidations that follow such cleavage. It is clear that some of the reducing substances present in cells are very readily oxidised, while others, like the carbohydrates and fats, are much more stable and resistent to oxidation. According to what is perhaps the most reasonable view, the oxidation of the readily oxidisable substances occurs in the manner just described with the liberation of nascent oxygen, which is capable of oxidising the more stable substances such as fat and glucose. Or, to state it somewhat differently, the readily oxidisable substances split the oxygen molecule during their own direct oxidation, and by virtue of this cleavage, with liberation of nascent oxygen, these direct oxidations are the indirect means of oxidising fats and carbohydrates It appears, however, at least in the case of glucose, that the presence of a special ferment is essential in some way to oxidation ; and this may be true also in the case of fats.

A failure in the oxidative functions of the cells leads to the

impaired combustion of sugar and its appearance in the urine. Similarly a failure to burn sugar or fat, or both, may lead to the appearance of pathological organic acids in the urine.

Processes of hydration and dehydration, like those of oxidation and reduction, play a part in augmenting or decreasing the toxic properties of certain substances belonging normally to the animal organism. For example, the conversion of albumins into albumoses and peptones is a process involving a cleavage of the proteid molecule, together with the taking up of the elements of water or the hydroxyl group OH. These proteid products of digestion are well known to exert a toxic influence on the nervous system when introduced directly into the circulation. In health bodies of this character cannot be found in the blood, and it is known that even after peptones or albumoses have been experimentally introduced into the blood-stream they quickly disappear. We are justified in making the inference that these substances become converted into some harmless nutritive proteid through the action of special cells. It has been generally thought that this substance is serum albumin, and that it is produced through changes just the reverse of those by which native albumens are converted into albumoses and peptones, that is, a process of dehydration. It has also been generally thought that this conversion is accomplished chiefly, if not wholly, by cells forming a part of the structure of the intestinal walls in the course of the passage of the digestive products from the intestine into the vascular system. Some writers have attributed this action to the epithelial cells themselves; others have referred it to the lymphoid cells and leucocytes which crowd the intestinal walls during digestion. While there are objections to these views there is little doubt that in some way the albumoses and peptones, which possess toxic properties in some degree, are ultimately converted into the nutritive blood proteids normally present in the blood.

I wish now to call your attention to the important part which synthetic processes play in ridding the organism of substances possessing toxic properties. You are of course well aware that the human body, like that of vertebrate animals in general, is characterised by its very active decompositions, which are usually attended with oxidation, and through which the body maintains its animal heat and its muscular power. These destructive and disruptive

occurrences are, as you know, distinctive of animal life as compared with the life of plants. Plants are capable of utilising very simple substances, and of uniting them to form substances consisting of much more complex molecules. Thus from carbonic acid and water they manufacture the carbohydrate materials which they store so plentifully. Even their complex proteids are built up from comparatively simple molecules: from ammonia, which they get from soil, and from nitrites, which have been formed by the nitrifying bacteria of the soil. But the distinction between animals, as disruptive agents, and of plants, as synthetic organisms, must not be too sharply drawn. Although the disruptive activities of animals are highly characteristic, and preponderate over those of the constructive type, syntheses go on to a very considerable extent. These syntheses are not only of much importance in building up various constituents of cells, but they are also capable of taking on a detoxicating action. Among the prominent physiological syntheses which are constantly going on are the formation of fat from carbohydrates and the formation of hæmoglobin. These are pre-eminently nutritive syntheses. The detoxicating syntheses are probably more numerous and more complex than we are fully aware. Some of these processes have been carefully studied—*e.g.* those syntheses which involve the combination of aromatic substances with sulphuric acid with the formation of the so-called ethereal sulphates. Two of these ethereal combinations of sulphuric acid are known to possess considerable practical importance. One of these relates to phenol, another to indol. Both these substances are formed in the intestines as a result of the cleavage of proteids. Frequently they are formed in considerable excess. They possess toxic properties, and when brought into contact in their unchanged form with the elements of the nervous system are capable of setting up marked derangements of function, and probably even histological changes. But the nervous system is screened from the action of these bodies and others of a similar character through a combination with sulphuric acid. This sulphuric acid is furnished by the organism, perhaps chiefly by the liver cells. The importance of this synthesis to the organism lies in the fact that the new-formed compounds are far less toxic in their action than either phenol or indol. I have already mentioned to you that in the case of indol there is first an oxidation to indoxyl,

and it is this radical which combines with sulphuric acid to form an indoxyl sulphate of potassium. In the case of phenol no such intermediate oxidation is known to occur.

There are other acids than sulphuric that are capable of pairing with aromatic bodies like phenol and indol, probably with the result of lessening the toxic action of the latter. One of these acids is glycuronic acid ($COOH,(CH.OH)_4CHO$), which represents an early stage of oxidation of glucose. In health the amount of this acid which finds its way into the urine in aromatic combination is small. When, however, the amount of sulphuric acid does not suffice to pair with all the aromatic substances in the organism, glycuronic acid fills the requirements, and may be excreted in considerable amount. It is also well known that after the administration of large doses of camphor the urine contains a large amount of glycuronic acid. Indeed, recent unpublished experiments by Halsey show that enormous quantities of glycuronic acid, equivalent to the carbohydrate moiety of the proteid molecule, are eliminated as camphoglycuronic acid under certain conditions. Naphthol, borneol, menthol, turpentinol, and many other substances pair with glycuronic acid.

In studying the manner in which the cells of the body act upon phenol I observed a highly interesting phenomenon. This is the capacity of the cells to tie the phenol to their protoplasm in some loose combination, pending the time required to produce the sulphuric acid necessary to effect the synthesis just mentioned. If we introduce a certain quantity of phenol into the circulation of a rabbit, and bleed the rabbit to death, we find that the liver contains phenol at first, but that this phenol soon disappears if the removal of the liver be delayed. I found also that the liver pulp outside the body has the capacity to unite with phenol in such a way that the phenol cannot be recovered by distillation. That this union of the cell protoplasm with phenol is only temporary is indicated by the fact that all the phenol introduced can be quickly recovered through the urine, united to sulphuric acid. This recovery of the phenol would not be possible were the combination with the cells a stable combination. It was found that the behaviour of the cells towards indol is similar, and we may suspect that there are many toxic agents which are thus held in loose union to cell protoplasm. Our observations on the union of the cell

protoplasm with phenol and indol are of interest in connection with the views of Ehrlich as to the union of bacterial toxins with the side-chains of protoplasm. It is possible that the complex proteid molecule is able to modify the toxic properties of many substances by effecting a union between certain side-chains and these toxic substances, and this is probably one of the most important defences of cell protoplasm.

Another synthesis of great interest physiologically, though of somewhat less interest than phenol and indol from the standpoint of pathology, is the combination of benzoic acid and glycocoll. Whenever benzoic acid enters the body (from vegetable food-stuffs) it unites with glycocoll to form hippuric acid, and is excreted as such by the urine. This highly interesting synthesis is thought to occur mainly in the kidneys—at least in the case of dogs. In the human subject it is not unlikely that other cells than those of the kidney contribute to effect this union. To what extent this particular synthesis can be regarded as operating to detoxicate the organism is a question which cannot be definitely answered, since it is not clear that benzoic acid, in the ordinary quantities in which it is taken into the body, exerts any toxic action.

A much more important synthesis is that which occurs in the formation of urea from the nitrogenous waste of cells throughout the body. In the course of the physiological breaking down of the protoplasm of cells the proteid molecule normally becomes decomposed in such a way that a portion of its nitrogen eventually exists in the cell in the form of ammonia. This ammonia is wholly a waste product, and represents the last stage of metabolism. The quantity of ammonia formed in this way is very considerable, and is important on account of its decidedly toxic properties. It is thought that the ammonia thus formed in the different tissues is liberated as such, to be combined very soon afterwards into urea, through union with the carbonic acid of the blood. The formation of urea from ammonium carbonate by dehydration is expressed by the following equation :—

$$(NH_4)_2CO_3 - 2H_2O = CO(NH_2)_2.$$

There is no doubt whatever that one of the ways in which urea arises is from a union between ammonia and carbonic

acid. It is not entirely clear, however, just what are the intermediate stages of the transformation. It is probable that ammonium carbonate, or possibly carbamic acid, is formed as an intermediate step, the former process being, I think, the more likely. There is no doubt that this process goes on, especially in the cells of the liver ; and some investigators believe that it occurs there exclusively. But there is satisfactory experimental evidence for believing that the liver is not the exclusive seat of this synthesis, and that it occurs to a less extent in the muscles, and perhaps in the tissues generally. These interesting questions as to the nature of the intermediate products in the formation of urea, and of the seat of the urea synthesis, are somewhat aside from our principal theme. What I wish here to emphasise particularly is the fact that urea, though by no means devoid of toxic properties, is much less poisonous to the organism than ammonia. Hence the synthesis of which I have been speaking is to be regarded as distinctly protective to the body. Urea is not only less poisonous than ammonia, but it is less poisonous than the salts of ammonia, *e.g.* the ammonium carbonate. It is not only less poisonous than ammonium carbonate, but possesses very remarkable diuretic properties. As a result of these diuretic properties, urea is removed from the blood by the kidney almost as soon as it is formed, and, as a consequence, the percentage of urea in the blood is, in health, remarkably low.

I wish now to say something about a noteworthy synthetic process to which investigators have called attention in recent years. This is the process of methylation. The methyl group is a radical of methane or marsh gas. Now this group (CH_3) appears to be furnished by certain radicals in the protoplasm of the cells, and under favourable conditions the methyl group is united to substances which are brought into the body. This process of methylation is carried on, for instance, when the substance called pyridin is brought into the organism. Pyridin is nothing more than benzene in which one CH group has been replaced by nitrogen. The pyridin introduced into the body becomes methylated through a combination with the methyl radical, and finds its way into the urine as methyl pyridin. A special interest attaches to this methylation of pyridin, because many of the alkaloids contain a pyridin radical. It seems probable that the methylation process at least

facilitates the elimination of pyridin, and it may have some influence in depriving it of toxic properties.

A similar process of methylation occurs when the metals selenium and tellurium enter the body. The interest attaching to the fate of these metals is mainly theoretical, inasmuch as they seldom find their way into the organism, except in connection with experimental studies. It is, however, worthy of note that a certain proportion of the tellurium that enters the body is again excreted by the lungs and urine in the form of methyl tellurium.

Before taking leave of the subject of the chemical defences of the body against poison I wish to call your attention to the arrangements by which it is possible for the organism to neutralise any excess of acids that may be formed within the body, or that may be introduced from without. I have already emphasised the importance of the alkalinity of the blood for the carrying on of oxidative and other vital activities in the cells, and have tried to impress on you the gravity of any distinct diminution in this alkalinity. In health the alkalescence of the blood probably varies only within narrow limits, and whenever it happens that owing to defective oxidations certain acids which should be burned accumulate in the organism, it is of the first importance that this acid should be disposed of in some way which will not involve any reduction in the alkalescence of the blood.

In the course of disease it happens not infrequently that organic acids either are formed in excessive amounts in the course of metabolism, or, what is more likely, fail to be burned as in health. What becomes of this excess of acid? How does the organism protect itself against the consequences that must arise from the presence of a free acid in considerable amounts? Any free acid which is formed is at once neutralised by combination with certain bases, which are always available for this purpose. We are not altogether clear as to the details of this process of neutralisation, but it is evident that there are at least two sources of alkali which can be used for this purpose. One of these is the carbonate, especially the sodium carbonate, of the blood, to which the blood largely owes its alkalescence. It is easy to see how the introduction of a free acid into the blood would be followed by a union of this acid with the alkali of the carbonate, accompanied by a simultaneous dis-

placement of carbonic acid and its liberation by the lungs. But such a displacement of carbonic acid would necessarily somewhat reduce the alkalescence of the blood, and this is precisely what happens in some acid intoxications, as, for example, in the course of the intoxication which exists in diabetic coma, where the alkalescence of the blood becomes distinctly reduced through the accumulation of β-oxybutyric acid and other organic acids. The sodium derived from the carbonate which contributes to the neutralisation of the acids is eliminated by the kidneys, and thus becomes the means of ridding the organism of an injurious substance. Probably it happens in the course of every acid intoxication that a certain amount of the carbonate of sodium or other alkaline salt is acted upon in the manner that I have just described. But it is certain that this particular mode of neutralising an acid may sometimes play a comparatively insignificant *rôle*, and may lead to only an unimportant reduction in the alkalescence of the blood. This is because there is another base which is constantly available in very considerable quantities for the purpose of neutralising any excess of acid that may arise in the organism. This base is the ammonia to which I have already referred in speaking of the origin of urea. There is good reason to believe that the introduction of an unusual quantity of acid into the blood is followed regularly by a union of at least a portion of this acid with the ammonia, which, under normal circumstances, goes to form urea. Or, to put it somewhat differently, a certain amount of the ammonia which normally enters into the formation of urea becomes intercepted by the presence of an acid, with which it enters into combination. Two results follow from this arrangement. One of these is the appearance in the urine of an increased amount of ammonia. In health the urine contains only a small amount of ammonium in acid combination, not more than from 2 to 5 per cent. of the total nitrogen of the urine being in this form. Under the conditions of which I am speaking the quantity of nitrogen of ammonium may reach 10, 15, or even 25 per cent. of the total nitrogen of the urine. The other result which follows from this pathological diversion of ammonia is a corresponding reduction in the quantity of urea which is formed.

It is certain that under some conditions other bases besides sodium and ammonium are employed in the neutralisation

of excessive quantities of acid. Thus, in diabetes the body may be robbed of some of its calcium and magnesium, which are sacrificed in the cause of neutralising acids which are present in pathological amounts. Potassium is also removed whenever sodium is excreted in pathological amount, but usually this base suffers less than sodium.

I have been able to sketch for you only some of the more important features that enter into the process of neutralising acids. Investigators still have much to learn in regard to particular types of acid intoxication in connection with the different clinical manifestations of disease. We know something about the conditions that exist in severe cases of diabetes, where an acid intoxication of the most extreme type frequently exists. The urine contains large amounts of organic acids, not only during the state of diabetic coma, but for a considerable time before the onset of grave cerebral symptoms. As I shall point out to you in discussing diabetes, the prognosis in this disease is largely determined by the quantity of organic acid which the patient excretes.

The importance of acid intoxications is, however, by no means limited to diabetes, although there is no pathological state in which such large quantities of acid are neutralised by ammonia and other bases. Small quantities of organic acid pass from the blood into the urine in cases of dilatation of the stomach and in some other disorders of digestion. Observations made in my laboratory indicate that in all early cases of arthritis deformans noteworthy quantities of organic acid are regularly found in the urine. It is convenient to use the term *acidosis* to designate the slighter grades of acid intoxication.

At the risk of devoting relatively too much time to the subject of intoxication by acids, I wish to give you some idea of the means which we possess of determining whether such an intoxication exists in a given case. One of the best evidences of such a disturbance is the increase in the ammonia of the urine, to which I have already referred. It is not quite clear, however, whether an increase in ammonia in the urine is to be regarded merely as an indication of poisoning by acid. In some diseases of the liver there is extensive destruction of the liver cells, and it may well be that under such conditions the liver cells are unable to bring about with their full energy that synthesis of ammonia and carbonic acid which results in the formation of urea. If

this were the case it is easy to see how an excess of ammonia in the urine might be referable to this defective synthetic power in the liver, rather than to an acid intoxication. But this possibility has only to be considered where there is extensive damage to the liver cells, and there is no conclusive evidence that such failure in synthetic activity occurs even under these conditions.

If it could be shown that the cells of the liver under some conditions are unable to perform the synthesis of urea, we should have to find an explanation of the appearance in the urine of ammonia united to organic acids. It seems entirely in accordance with what we know of the hepatic functions to suppose that any failure in cell activity resulting in the impaired synthesis of urea would also lead to the impaired combustion of the organic acids which in health are burned by the hepatic cells. The unburned acids would serve to neutralise the ammonia and carry it out by the urine. But I consider it far more likely that the primary difficulty consists in the failure of the liver to burn organic acids, and that in states of acid intoxication ammonia appears in the urine because it has been diverted from the synthesis of urea to neutralise acid, and not because the liver is incapable of carrying on this fundamental synthetic activity.

It also happens at times that an acid intoxication exists where the ammonia of the urine is not distinctly increased, and this is probably owing to the fact that in such cases it is sodium or some other base that is united to the acid. It is thus clear that the nitrogen of ammonia in the urine is not an altogether trustworthy guide to the existence of a poisoning by acid. In order to obtain a satisfactory idea of the extent of an acid intoxication it is necessary to carry out a somewhat laborious chemical process. This process consists in determining the chief acids of the urine and the chief bases. The chief acids are sulphuric, phosphoric, hydrochloric, and uric acids. The chief bases are sodium, potassium, calcium, magnesium, and ammonium. In conditions of health the acids are almost exactly neutralised by the bases mentioned, although there is normally a slight excess of acid (see Lecture XII.). Now, whenever there is an intoxication through some acid formed in the body, which is not one of the four acids just mentioned, that acid becomes neutralised, as I have already indicated to you,

through the agency of a base furnished by the organism. This detoxicating base is always, so far as we know, one of the five just mentioned. Hence it happens that when we find that the sum of the bases is in excess of the sum of the acids, which I mentioned, this excess can be regarded as positive evidence of the presence in the urine of some unknown acid, which is the factor in producing intoxication. It sometimes happens, as in diabetic coma, that the bases are greatly in excess of the four acids. In this instance the intoxicating acid is mainly oxybutyric acid; but diacetic acid is also concerned, and probably there are other oxyacids allied to oxybutyric.

I must not quit our subject without mentioning to you a study indicating how prominent a part the leucocytes take in protecting the organism against a highly injurious inorganic poison. Quite recently a French investigator, Besredka, has found that subcutaneous injections of arsenious acid into rabbits, in doses not quite large enough to prove fatal, are followed by a temporary diminution in the number of polymorphonuclear leucocytes in the blood, which is succeeded rapidly by a much more prolonged hyperleucocytosis in which the polymorphonuclear leucocytes chiefly are increased. If the leucocytes be collected from the blood by suitable methods during this period of hyperleucocytosis, and subjected to analysis, they are found to contain arsenic. An interesting feature of these experiments is the fact that when the poison was injected in sufficiently large amount to cause death the initial hyperleucocytosis was not followed by an increase in the number of leucocytes, and that under these circumstances the arsenic was not found in the white blood cells. It seems clear that the appropriation of the arsenic by the leucocytes is closely connected with the recovery of the poisoned animals. Further experiments were made which indicate that a certain degree of immunity can be established against doses of arsenic which ordinarily prove fatal by means of smaller injections. It is also claimed that this immunity is brought about by the formation of special antitoxic substances, but further studies are necessary to prove that this is the case. It appears unlikely that inorganic poisons like arsenic and other heavy metals are capable of inducing immunity through the production of antitoxic substances. The formation of such antitoxic substances has been shown

to occur in response to the stimulus of highly complex substances such as poisonous phytalbumoses (ricin, abrin, crotin, phallin), bacterial secretions (staphylotoxin, pyocyaneous poison), and toxic animal secretions (snake poison), which have a close chemical affinity to the proteids. The measure of immunity to arsenic and other inorganic poisons probably depends on wholly different chemical defences.

I have referred many times to-day to the toxic properties of different substances, but have not attempted to define what we mean by a poison. It seems to me that one ordinarily thinks of a poison as a substance invariably injurious to the organism. We are apt to lose sight of the fact that many of the bodies called poisons sometimes act injuriously, sometimes not, according to circumstances. The diphtheria toxin, so toxic to the horse and other animals, leaves the rat unharmed. Contact with the poison ivy sets up an intense dermatitis in one person, but is without effect upon another. Small doses of indol by the mouth render one person nervous and irritable, but have no influence on another. Arsenic and morphine are highly toxic to subjects unused to the effects of these drugs, whereas persons habituated to their use are relatively insensitive. Alcohol and many of the lower fatty acids are powerful irritants when given in concentration, but these same bodies possess some food value when absorbed under certain conditions. Thus you see we must be prepared to consider many factors which modify the poisonous properties of any given substance, rendering it sometimes toxic, sometimes relatively or wholly harmless. We have to bear in mind that the toxic effect of a given substance depends on the individual characteristics of the cells of the organism as well as on the chemical constitution of the poison.

I have now brought to your notice the chief processes by which the organism is able to combat the various poisons by which it is menaced in the course of disease. I do not mean to give the impression that there are not other important ways in which the action of poisons is combated. But I think I have given examples of the more important conservative reactions about which we possess some knowledge. There is no doubt that intelligent research will in time give us new methods of investigation, new points of view, and, consequently, important additions to our knowledge of the chemical defences of the body.

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LECTURE II

THE CHIEF FOOD-STUFFS AND THEIR FATE IN THE BODY IN HEALTH AND DISEASE.—THE CARBOHYDRATES AND FATS

Chemical structure of the carbohydrates—The hexoses or monosaccharides; aldoses and ketoses—The disaccharides—Pentoses—Starches—Salivary digestion of starches—Action of gastric juice—Pancreatic digestion—Carbohydrates are burned to carbon dioxide and water—Glycuronic acid—Storage of carbohydrates in liver and muscles as glycogen—Production of fat from carbohydrates—Potential energy of carbohydrates and other food-stuffs—The calorie—Caloric expenditure of the human body—Influence of carbohydrates on excretion of acetone—Carbohydrates and fatigue of muscle—Experiments of Dr. Lee—Carbohydrates as food-stuffs—Cane sugar—Milk sugar—Maltose—Effects of carbohydrate excess—Starches—Cellulose—Saccharin as a substitute for sugar—The fats—Chemical constitution of neutral fats—The triglycerides, stearin, palmitin, and olein—Digestion of fats—Their absorption as fatty acids and soaps—Fate of the fatty acids and soaps after absorption—Caloric value of neutral fats—Substitution of fats for carbohydrates in the dietary—Saving of proteid waste by carbohydrates and fats—Influence of fats on absorption of salts of calcium and magnesium—Influence of fat on the nervous system—Use in constipation—Contra-indications to the use of fat—Fat starvation and serous atrophy of fat—Fatty infiltration—Origin of sugar from fat—Fats as food-stuffs—Milk fat; butter—Emulsions—Chocolate—Subcutaneous injections of olive oil.

To-day I propose to call your attention to certain facts relating to the food-stuffs and their fate in the human organism in conditions of health and disease. We must regard the human body as a machine which obtains energy through the physiological decomposition and combustion of various kinds of food, and it is exceedingly important that you should have a clear conception both of the normal fate of these food-stuffs and of the derangements in nutrition and in the production of energy that arise when the assimilation of such food-stuffs is no longer normal.

There are three principal classes of food-stuffs which it is necessary for us to consider—the carbohydrates, the fats, and the proteids. In addition to these we have to consider the albuminoids and the inorganic elements of food, *e.g.* the various salts and water. Although these inorganic substances do not yield energy through their decomposition, the various salts and water are highly important to the organism through their physical and chemical properties. It will therefore be necessary to devote special attention to them after discussing the chief organic food materials. The albuminoids are represented chiefly by gelatine, to which special reference will be made.

Until recent times it has been customary to describe the carbohydrate molecule as characterised chemically by containing carbon, hydrogen, and oxygen, the oxygen and hydrogen being present in the proportions in which they are found in the molecule of water. Such a description is inadequate because it gives us no conception of the manner in which the atoms of carbon, hydrogen, and oxygen are actually linked. The researches of the distinguished chemist Emil Fischer have thrown new light on the chemical structure of the carbohydrates. We now know that the sugars which contain six atoms of carbon in the molecule, and are hence called hexoses, are divisible into two important groups, according to their chemical structure. In one group the linking of the atoms is such that the molecule contains the group CHO. You know that this group is characteristic of the class of bodies known as aldehydes. Thus formic aldehyde is H.CHO, acetic aldehyde CH_3CHO. The sugars that are built on this type are called aldoses, in order to recall their aldehyde structure. The way in which the atoms are linked in the case of glucose, a typical sugar of this kind, is seen in the following graphic representation :—

$$CH_2(OH).CH(OH).CH(OH).CH(OH).CH(OH).CHO$$

The other group of hexoses is characterised by a different arrangement in the linkage of the atoms by which the two ends of the chain of atoms consist of symmetrical groups as in the case of the bodies known as ketones, of which acetone is a familiar example. Notice the constitution of the

acetone molecule $CH_3.CO.CH_3$. Owing to their structural peculiarity these bodies have been called ketoses. Lævulose, a variety of sugar closely related to dextrose, but differing from it in rotating the plane of polarisation to the left instead of to the right, is a typical example of a ketose. Its structure may be represented as follows :—

$$CH_2(OH).CH(OH)CH(OH).CH(OH)CO.CH_2(OH)$$

The empirical formula for the ketoses and aldoses is $C_6H_{12}O_6$. These hexoses, containing six atoms of carbon in the molecule, are also known as monosaccharides to distinguish them from the more complex group of sugars known as the disaccharides. The disaccharides, of which the most important are cane sugar, milk sugar, and maltose, are made up by the union of two molecules of monosaccharides. The following table shows the products that arise when different polysaccharides break up into monosaccharides :—

Cane sugar ($C_{12}H_{22}O_{11}$) + H_2O
= Glucose + Glucose ($C_6H_{12}O_6$)

Milk sugar ($C_{12}H_{22}O_{11}$) + H_2O
= Glucose + Galactose ($C_6H_{12}O_6$)

Maltose ($C_{12}H_{22}O_{11}$) + H_2O
= Glucose + Glucose

You will notice that all these disaccharides have the same empirical formula, namely, $C_{12}H_{22}O_{11}$, and that they break down into monosaccharides on taking up one molecule of water. You will observe also that the various carbon atoms entering into the structure of the sugars are connected by single affinities or links. In consequence of a relatively weak connection between the carbon atoms the molecules of sugar break down readily into a simpler substance containing smaller numbers of carbon atoms in the molecule.

There are two decompositions which occur in the monosaccharides which I wish you to remember, as they have important bearings upon the origin of some pathological products with which we meet in the course of derangements of digestion. One of these decompositions is the breaking down of glucose under the action of the yeast ferment into two molecules of alcohol and two molecules of carbonic acid. The second is one which occurs in the body under the

influence of the lactic acid bacilli and certain varieties of the colon bacillus. The process is known as lactic acid fermentation. The equations which express these decompositions I shall give you when speaking of excessive fermentation in the digestive tract.

Besides the classes of sugars which I have just mentioned there are others in which the molecule contains five instead of six atoms of carbon, and which are hence known as pentoses. Arabinose and xylose, or wood sugar, are examples of pentoses, and are represented by the formula $C_5H_{12}O_6$. Pentoses occasionally occur in the urine after the use of fruits, in some cases of chronic morphine poisoning and in some instances of diabetes. They are of little importance compared with other classes of carbohydrates.

The starches form, perhaps, the most important class of carbohydrates, because of their abundance in our foods. The precise constitution of the starch molecule is not yet understood, but it is known that the molecule contains the group $C_6H_{10}O_5$, taken a number of times. The starch molecule is thus considerably larger than the largest sugar molecule. Under the action of dilute acids and certain ferments the starches undergo a process of hydration and cleavage, through which sugars are formed. Starch, dextrin, glycogen, and cellulose all contain the group $C_6H_{10}O_5$.

Only a small portion of the carbohydrates taken with the food are in a form fitted for immediate absorption. The greater part exists as starch, as, for example, in potatoes, bread, vegetables, &c., and has to be prepared for absorption by passing into a soluble state. This process, as already mentioned, is one of cleavage and hydration of the starch molecule, which leads to the formation of disaccharides and monosaccharides. It may be noted that the carbohydrate glycogen, which is stored in the liver and muscles for consumption by the cells of the body, is prepared for utilisation by a similar process of conversion into dextrose.

The ferments which split the starch molecule into sugars are furnished by the saliva and the pancreatic juice. The process is begun in the mouth through the ptyalin of the saliva. The change is not carried very far, and only traces of glucose result from digestion in the mouth. The products formed there are soluble starch, certain forms of dextrin, and maltose. Although the conversion of starch is only begun in the mouth, the thorough mastication of the food and its

insalivation are important in that they favour an early and considerable absorption of carbohydrates from the digestive tract before there is time for excessive fermentation.

The gastric juice precipitates the diastasic starch-splitting ferment, so that the process of digesting carbohydrates is quickly though not immediately checked in the stomach. When the partially digested starches come into contact with the pancreatic ferment known as amylopsin an energetic process of conversion begins. But even this does not lead to a complete transformation into dextrose or glucose. The final conversion into dextrose or glucose is thought to occur in the epithelial cells of the intestine, and to some extent in the blood through the action of a ferment there.

Most of the carbohydrate material which is absorbed passes by the mesenteric veins to the portal system. Probably less than one per cent. goes through the lymphatics and the thoracic duct into the venous system.

In health the carbohydrate food that is eaten does not appear in the fæces, although of course a certain amount of cellulose is always to be found there if vegetable food is used. The fact that there is no soluble carbohydrate material in the fæces does not enable us to infer that it is all absorbed and utilised. Even in health there is always some waste of energy and potential from the fermentation of the carbohydrates. In the course of this fermentation acetic acid, lactic acid, butyric acid, alcohol, &c. may be formed. In conditions of disease the amount of caloric potential that is lost through excessive fermentation may be so considerable as to distinctly impair nutrition. I shall have more to say on this subject when we come to discuss the processes of fermentation and putrefaction in the intestine.

The blood of the portal vein contains carbohydrate material in the form of glucose. In the body this glucose is burned, in part at least, to carbonic acid and water, with liberation of energy, which may be expended either as animal heat or as muscular power. I wish to call your attention to the fact that the intermediate stages in the burning of glucose are not understood. The first product of the oxidation of glucose is probably glycuronic acid. You remember that glucose or dextrose has the formula $C_6H_{12}O_6$. If a molecule of water be removed from this body there results $C_6H_{10}O_5$. If now oxidation takes place, with the introduction of two atoms of oxygen, the resulting body has

the formula $C_6H_{10}O_7$, which represents glycuronic acid. This glycuronic acid enters into a synthetic combination with certain aromatic bodies, such as phenol, and a portion of it is excreted by the organism in this form. Probably the greater part of the glycuronic acid is broken down into less complicated molecules on the way to the production of carbonic acid and water, which represent the final products of oxidation. It has been claimed that the lactic acid of the muscles, sarco-lactic acid, is one of the intermediate products of oxidation, but the evidence in favour of this view is not wholly satisfactory.

Carbohydrates are usually absorbed in excess of the immediate need of the organism. They are then stored in the liver and muscles in the form of glycogen, to be called on when they are required. When required for nutritive purposes the glycogen of the liver is converted into glucose. The blood never contains glycogen except in such small quantities as form part of the leucocytes. Carbohydrate material is known to be present only as glucose, and, owing to a very finely adjusted regulatory mechanism, the percentage of sugar in the blood remains remarkably constant in health without reference to the diet. A very slight increase above the normal quantity of sugar in the blood leads to its excretion by the urine, and thus it happens that the normal sugar content of the blood is never exceeded in a considerable degree. When starvation occurs the blood continues to hold sugar, but this comes from a diminishing supply of glycogen in the liver, and after a time, when the supply is exhausted, from a decomposition of the proteid constituents of the tissues. But even in starvation the glycogen of the liver and of the muscles is probably not wholly consumed.

I have already told you that a portion of the carbohydrate material of the body is burned and split into carbonic acid and water, with a yield of energy, especially animal heat. Under some conditions all the carbohydrate food available in the organism is utilised for this purpose, but commonly there is an excess in the body above what is required for the maintenance of animal heat and muscular power. This excess then becomes converted into fat. I referred to the formation of fat from carbohydrates in speaking to you about the synthetic activities of the cells of the body. I called your attention to the fact that the

process involves a union of several molecules of carbohydrate for the formation of one molecule of fat, and that simultaneously with this polymerisation there is also a process of reduction by which oxygen is removed. We do not know at present in which cells of the body this synthesis occurs. Nor do we know anything about the actual chemical conditions under which it takes place. It is, however, a process of the greatest importance, for it enables the body to lay up a reserve store of fat, to be drawn upon in times of need. Were the body incapable of forming fat from carbohydrate material, it would be dependent for its fat upon the fats contained in the food. Normally the formation and storage of fat are in a considerable degree independent of the introduction of fats into the body.

But what proof have we that carbohydrates are, in fact, capable of forming fat? The proof is that young animals fed on proteids and carbohydrates grow and increase their store of fat, notwithstanding there is no fat in the food. You will perhaps ask if it is not possible that this increase in fat depends on the non-nitrogenous or carbohydrate moiety of the proteid molecule; for, as you are probably aware, there is no doubt that the proteids are capable of yielding carbohydrate material when certain cleavages take place. There is little doubt in my mind that the body is capable of making fat from this carbohydrate portion of the proteid molecule; but I can easily give you evidence that there is not enough carbohydrate material in the proteids to account for the quantity of fat which is laid up by animals on a diet of carbohydrates and proteids. This evidence consists in the fact that the quantity of carbon in the fat which is laid up on such diet has been shown to be distinctly in excess of the carbon which is present in the proteids that are taken. This excess of carbon in the fat can therefore arise only from carbohydrates. I have referred to this utilisation of carbohydrates with some degree of detail because, as you will see later, it is essential to know something of the normal fate of these important food-stuffs before you can appreciate the consequences of their deranged assimilation.

I have just told you that the carbohydrates are largely utilised in the production of animal heat. By means of very carefully conducted experiments it has been possible to determine just how much energy the carbohydrates and other food-stuffs are capable of yielding. This energy is, in

part, utilised in the performance of muscular work; but inasmuch as the greater part of the energy of the organism is expended as animal heat, it is convenient to calculate the potential energy of the food-stuffs in terms of heat units. The unit employed for this purpose is the calorie. A calorie is the amount of heat required to raise the temperature of one gram of water one degree centigrade. This is the ordinary or small calorie (cal.). In dealing with the heat production of the human body it is convenient to use a larger unit than the small calorie. Such a unit exists in the large calorie (Cal.), which represents the amount of heat required to elevate the temperature of 1,000 grams of water, or one kilo., one degree centigrade. One large calorie is thus equal to 1,000 small calories.

If carbohydrate food or any other form of food be burned outside the body in an apparatus devised for the purpose, it is possible to determine exactly how much heat is liberated when a given quantity of the food-stuff is burned into its simplest form. Now it has been shown that the amount of energy yielded by the burning of the different food-stuffs outside the body corresponds closely to that which is yielded when they are burned inside the body, assuming, of course, that the same ultimate products of combustion are reached in the two cases. These products, in the case of carbohydrates and fats, are carbonic acid and water.

When one gram of carbohydrate is burned in the body it yields very nearly four and one-tenth large calories. When one gram of proteid food is utilised in the organism it yields almost exactly the same amount of energy as one gram of carbohydrate material. But when one gram of fat is burned the yield of energy is very much greater; it is, in fact, more than twice as great as the yield of heat energy derived either from the carbohydrates or the proteids. One gram of fat yields about nine and five-tenths large calories. The reason for this greater yield of energy from fat will be quite clear to you when we consider the chemical constitution of fatty substances.

You are now in a position to understand the caloric needs of the human body. A man weighing 70 kilos. (154 lb.) expends about 2,500 large calories in twenty-four hours when he is taking moderate exercise. Where there is active exercise the expenditure of energy is 10 or 15 per cent. greater than this. Where there is a condition of rest

the expenditure in heat units is 10 or 15 per cent. less. If the organism does not receive a sufficient quantity of food to yield the energy which is expended as heat, the body consumes its own tissues, especially its subcutaneous fat, in order to meet the caloric requirements pertaining to the maintenance of life processes. How much food, and what kind of food, is required to yield the necessary number of caloric units for the maintenance of a human body which performs a moderate amount of muscular work during twenty-four hours? The necessary energy would be supplied by a diet containing 100 grams of proteid with a yield of 410 large calories, 100 grams of fat with a yield of 950 large calories, and 400 grams of carbohydrate with a yield of 1,640 large calories. The total yield of caloric energy on this regimen would be 3,000 large calories, provided these different kinds of food were fully utilised for the purpose of heat production in the body. I say provided they were fully utilised because, as a matter of fact, a complete utilisation of food-stuffs taken into the body never occurs, and is practically impossible. It is impossible because a certain proportion of the proteids, carbohydrates, and fats taken into the organism is destroyed in the course of putrefactive and fermentative changes in the stomach and intestine, or is lost by the fæces. Thus smaller quantities of the various kinds of food are absorbed in a form suitable for the caloric needs than are actually introduced into the stomach. We may therefore deduct from 10 to 25 per cent. from the theoretical caloric yield of the food in order to estimate the actual amount of energy ordinarily derived from the food-stuffs. In diseases of the digestive apparatus, in which putrefactive and fermentative alterations in the food are in excess of the normal or usual amount, the loss to the organism in potential energy as expressed in calories may be much greater than just indicated for the normal body. It becomes necessary in such cases of excessive waste of food energy, through decompositions in the digestive tract, to compensate for this by taking into the body a considerably larger quantity of food than would normally suffice for the needs of the organism. You will now understand that when I tell you the yield of one gram of carbohydrate food is four and one-tenth large calories, or that the yield of one gram of fat is nine and three-tenths large calories, I am referring to the maximum theoretical

yield of energy, the actual net caloric units from the food in the form in which it is absorbed from the digestive tract being considerably less.

There are two physiological properties of carbohydrate food which have only recently been established, but which are of so much interest that I must at least bring them to your notice. One of these is the effect of carbohydrates on the excretion of acetone. The body called acetone, $CH_3CO.CH_3$, is believed to owe its origin partly to the decomposition of the proteids of the cells, and is found in the urine in pathological quantities whenever tissue waste is excessive, as in fever, diabetes, starvation, and various cachectic states. If we put a person on a diet of proteids, with little or no carbohydrates, the amount of acetone is increased considerably beyond the average normal quantity. If now we give this person an abundance of carbohydrates the acetone excretion is greatly diminished, or is checked altogether. This reduced excretion of acetone is probably to be explained on the ground that the carbohydrate food decreases the waste of cell proteid, but it is not clear why the acetone excretion is sometimes quite stopped.

The other property of the carbohydrates has reference to the fatigue of muscle. Very likely you are aware that during the activity of muscle more of the muscle glycogen is used up than when the muscles are at rest. This fact suggests that there is a close connection between the work of muscle and the combustion of carbohydrate material in the body. It fails, however, to show us how intimate is the relation between carbohydrates and the fatigue of normal voluntary muscle. This is a subject which has recently been ingeniously investigated by Professor Frederic S. Lee, of Columbia University. It occurred to Professor Lee that if the fatigue of muscle were really connected with the exhaustion of carbohydrate material the mere experimental removal of the carbohydrates from the body should give rise to the indications of muscle fatigue. Accordingly, by administering the drug phlorhizin, he swept the greater part of their carbohydrate material from the fasting cats which were used for these experiments. Phlorhizin, as you are probably aware, has the singular property of impairing the combustion of sugar and of permitting its escape into the urine, thus depriving the cells of the organism of their carbohydrate food.

The animals subjected to the action of phlorhizin during several days were killed, and the course of fatigue in the tibialis anticus was studied. It was found that this muscle, instead of giving from 800 to 1,000 contractions per minute on electrical stimulation, as a normal muscle should, gave only from 200 to 400. Moreover, the curves of contraction in the phlorhizinised muscle resembled the later contraction curves of normal muscle when undergoing fatigue, being low in height and showing a prolonged phase of relaxation: thus the remarkable fact was established that muscles from animals subjected to the action of phlorhizin behave like normal muscles in the late stages of fatigue.

Control experiments were made by Dr. Lee which indicate very clearly that the muscle fatigue observed after phlorhizin is not due to any specific action of the drug, but is referable to the loss of carbohydrate. One set of experiments was especially instructive in this connection. Animals were given phlorhizin during four days in the usual way. At the end of this period fifty grammes of dextrose were given by the stomach. Eight hours afterwards the animals were killed and the muscle fatigue was studied. It was found that the muscles gave 650 contractions, the first hundred of which were quite normal. Thus you see the administration of the sugar counteracted the effect of the phlorhizin and restored the muscle to a considerable extent.

The results obtained in these experiments harmonise well with the observation that muscle fatigue in healthy persons is delayed by the administration of sugar. They also give us a clue to the cause of the muscular fatigue that constitutes a clinical feature in such different conditions as diabetes, neurasthenia, and starvation. In diabetes the muscles are deprived of a part of their sugar because this sugar finds its way into the urine owing to imperfect combustion in the body. In many instances of neurasthenia there is an excessive fermentation of carbohydrates which perhaps leads to a pronounced reduction in the quantity of dextrose available for the use of the cells, including the muscle cells. This is, however, only a suggestion. In starvation the carbohydrate material available for the use of the muscles is greatly restricted, since the only sugar applicable to nutritive purposes is that derived from the breaking down of the proteids of the cells.

I do not mean to say that the muscle fatigue noted in

these different conditions depends wholly on the deprivation of sugar. Other factors are very likely co-operative. But I think we are justified in expecting undue fatigue of muscle whenever from any cause the muscles are deprived of their normal supply of carbohydrate material.

I wish now to say a few words about the different forms of carbohydrate food as we employ them in actual practice. It is by no means a matter of indifference in what form we advise our patients to take their carbohydrate food. I cannot give you elaborate descriptions of the composition of the different foods. These you can obtain from works on dietetics. I wish merely to point out certain principles which ought to guide us to an intelligent use of carbohydrates.

A certain amount of carbohydrate food can advantageously be taken in the form of sugar. The cane sugar, which we employ so freely for the purpose of sweetening the food, and the fruit sugar or lævulose, which is a constituent of fruits and honey, are useful forms of sugar. Like sugars generally these highly soluble carbohydrates are rapidly absorbed in conditions of health where digestion is active, and the stomach readily empties itself. But in pathological conditions, such as chronic gastritis or chronic gastro-enteric catarrh, the absorption of sugar may be considerably delayed. Under these circumstances fermentative changes almost always set in actively, and in a short time a large proportion of the sugar is broken down partly into alcohol and carbonic acid gas, in part into lactic acid.

In many of these patients the stomach becomes rapidly filled with carbonic acid gas after free indulgence in sugar, and I have known instances where the flatulence was accompanied in the course of half an hour or an hour by pronounced frontal headache. In some persons the free use of sugar is followed by diarrhœa, which is due very probably to the formation of lactic acid or acetic acid. Milk sugar undergoes alcoholic fermentation, and this fact is utilised in making kumyss and matzoon (zoolac). Pure yeast, however, which readily ferments dextrose, does not ferment milk sugar. This fact explains the greater readiness with which dextrose induces flatulence in some cases of gastritis. Maltose, which yields glucose in the course of digestion, arises from the hydrolytic decomposition of starch by means of malt diastase or ptyaline, or the pancreatic ferment called amylopsin. It forms the most important constituent of malted

milk, and is present in Mellin's Food and other foods largely employed in the feeding of children. Where the digestive processes are carried on normally, these soluble carbohydrates are very readily absorbed and utilised for conversion into fat. You will see many examples in the outdoor clinics of children who have received an excess of carbohydrate food. Many of these children are fat and weigh more than healthy children of the same age, but they are usually pale, their muscles are flabby, and they have less muscular endurance then children who have been properly fed. Less frequently you will find among adults similar examples of the detrimental influence of an excessive quantity of carbohydrate food. Such persons possess an abundance of soft adipose, but are deficient in muscular strength. A frequent peculiarity of patients who are receiving an excess of starchy carbohydrate is that the fæces show the effect of this excess by the presence of undigested starch, which undergoes active fermentation.

The effects of an excessive quantity of carbohydrate food in the form of starch are very similar to those that arise from sugar. Certain symptoms of this excess, especially flatulence, may be rather less marked. This is, perhaps, owing to the fact that the starch, being gradually converted into sugar, affords better opportunity for the complete absorption of the soluble carbohydrate material than where sugar is given in considerable quantities. In persons with normal digestive powers it does not seem to make much difference whether the food be taken in the form of bread, or potatoes, or rice—that is, in a form in which starch preponderates—or whether it be taken as it occurs in certain vegetables, such as peas, string beans, &c.—that is, as vegetables containing a considerable quantity of proteid. For most persons with chronic disturbances of digestion I think the starch is better tolerated and utilised in the form in which it occurs in vegetables. In almost all forms of gastritis or gastro-enteritis, acute or chronic, the digestion and absorption of the carbohydrates are impaired, and there occurs an excessive degree of fermentation in the digestive tract with the formation of the products that have already been mentioned. It is important in all chronic conditions where the digestion of starches and sugars is markedly impaired to reduce the quantity taken by the patient to a point where the symptoms of carbohydrate indigestion are

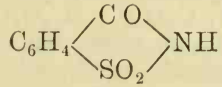
not prominent. It is best to begin by restricting the patient as regards the use of bread and potatoes. The removal of these articles of diet is often followed by a striking improvement in all the immediate symptoms of carbohydrate indigestion. It is a particular hardship to many persons to go without bread. The best substitute for bread is the biscuit known as Huntley & Palmer's Breakfast Biscuit. Although these biscuits contain some starch, they have a considerable quantity of dextrin, which is easily converted into dextrose. I am inclined to think that these biscuits owe their easy digestibility quite as much to their physical characteristics as to their chemical composition. They absorb water quickly and easily fall into small soft particles, a behaviour which must greatly facilitate the contact with the digestive juices.

Before concluding what I have to say in reference to starchy food I wish to say a word in regard to cellulose. This carbohydrate material forms a part of most vegetable food, and is especially abundant in the older and more fibrous vegetables. For the most part it passes through the intestinal tract with little change, and reappears in the fæces. It forms a valuable constituent of food for the reason that it helps to give bulk to the intestinal content in the lower bowel, and thus favours regular movements. The use of food containing a very small percentage of cellulose is apt to lead to constipation. On the other hand, an excessive proportion of cellulose is objectionable because the tough fibres act as irritants to the mucous membrane of the stomach and intestine. Chronic gastritis and other chronic digestive disorders are apt to be associated with constipation, and it is a temptation in such cases to prescribe a liberal or excessive amount of cellulose-containing vegetable food. It is easy, however, to cause distinct harm by so doing, and I wish to caution you against the free use of cellulose in such derangements. At one time certain biscuits, known as Dahl's Digestive Biscuits, which consist largely of bran, were much employed for the relief of constipation. Such cakes as these are useful when employed in moderation and in the absence of catarrhal derangements of the stomach and intestine; but I have known their use to do distinct harm through the mechanical irritation to which they gave rise. Cakes containing one part of bran with two or three parts of ordinary flour are frequently useful in the treatment of constipation. Perhaps the least objectionable

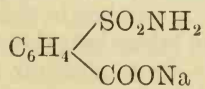
form in which we can give considerable cellulose is spinach. The spinach leaves should be very finely divided and cooked into the form of a thick soup. Taken in this way cellulose is rarely harmful. The presence of the spinach in the fæces is recognisable by the green coloration which it gives to them. Celery is also useful for the same purpose, but even when thoroughly stewed it seems to me less suitable than spinach.

A good deal more might be said about the properties of different kinds of carbohydrates and their utility in particular pathological states. I cannot, however, take the time to enter into these details, for which I refer you to works on dietetics. The points which I wish especially to impress upon you in connection with the carbohydrates are their value as sources of energy to the body, their relation to the contractility of muscles, their ready decomposition in the digestive tract into substances which are useless or even harmful, and the frequency with which disturbances of digestion arise from the use of excessive quantities of such food-stuffs.

Before passing to the consideration of the second group of food-stuffs allow me to say a word about a much-employed substitute for sugar—namely, saccharine, discovered by Professor Remsen, of the Johns Hopkins University. This body bears no resemblance whatever to any of the carbohydrates in its chemical composition, although it possesses a very sweet taste, much like that of cane sugar. The composition of saccharine is shown by the following graphic formula :—



You see that the body contains a phenyl group, C_6H_4, which indicates that it is a derivative of the aromatic series. You notice also that it contains a SO_2 group and a NH group. Soluble saccharine is the sodium salt of saccharin



It is soluble in 400 parts of water and twenty-five parts of alcohol, is about five hundred times as sweet as sugar,

and gives a sweet taste to 70,000 times its weight of water. In the moderate doses in which it is employed as a substitute for sugar it gives rise to no appreciable effects upon the organism. Artificial digestions are, however, slightly hindered by its action, and large doses injected into the circulation cause muscular depression and stupor. The only known objection to the moderate use of saccharine is that patients are apt to tire of it. This is owing to the fact that although it is intensely sweet its taste is not exactly that of sugar, and is displeasing to many.

I now wish to call your attention to the chief characteristics of the fats as elements of the food, and to the fate of fatty substances in the organism in health and in some pathological conditions. The fats as a class occupy a unique position among food-stuffs because of their high caloric value, to which I have already referred, on account of their easy digestibility without the formation of injurious products, and because of their influence in favouring the absorption of calcium and magnesium salts in the intestine.

The neutral fats are combinations of glycerine with certain of the higher fatty acids, of which the most important are stearic, palmitic, and oleic. Glycerine, you will remember, is a triatomic alcohol—that is, an alcohol containing three hydroxyl (HO) groups, as indicated by the following formula, $C_3H_5(OH)_3$. In a fat each of these three hydroxyl groups is replaced by a molecule of a fatty acid. The fats are sometimes called triglycerides of the fatty acids. The most important of them are tristearin or stearin, $C_3H_5(C_{18}H_{35}O_2)_3$, tripalmitin or palmitin, $C_3H_5(C_{16}H_{31}O_2)_3$, and triolein or olein, $C_3H_5(C_{18}H_{33}O_2)_3$. The molecule of these neutral fats contains more than 90 per cent. of fatty acid, the glycerine radical forming only a very small proportion. The lower fatty acids, such as caproic, butyric, &c., are met with both in the free form and combined with glycerine in some of the fats that are used as foods, especially in milk-fat. Free fatty acids, however, occur in animal fats only in small quantities. In general the vegetable oils, such as olive oil, are richer in these free acids.

The fats which are taken into the stomach undergo little change there. Such decomposition as may occur is the result of the action of bacteria and not of digestive ferments. The digestion of fat is carried on chiefly in the small intestine under the action of the steapsin ferment of the

pancreatic juice, which causes a breaking up of the fat molecule into glycerine and the corresponding fatty acids. The presence of the bile favours the action of the pancreatic ferment owing partly to its alkalescence, partly by reinforcing the tryptic ferment. The alkalinity of the bile aids in the emulsification of fats, which thus become more accessible to the action of the pancreatic ferment. When the fat molecule is split into glycerine and a fatty acid in the intestine, a variable portion of the fatty acid enters into combination with salts of the alkalis to form soaps of sodium, potassium, lime, and magnesium. In the upper part of the intestine it is thus possible to find fat in three forms—as neutral fat, as fatty acids, and as soaps. It is a question whether any of the neutral fat is absorbed as such by the epithelia of the intestinal mucous membrane. Although it has been generally taught that a certain amount of fat leaves the intestine as neutral fat, I think the evidence indicates that the epithelia are incapable of taking up even minute globules of neutral fat. The soaps and the fatty acids are readily absorbed, and probably all the fat is absorbed in one or other of these states. The bile helps very much in bringing about this absorption, for the fatty acids and sodium soaps pass readily into solution in the bile salts. The lecithin of the bile contributes to bring about the solution of the fatty acids and soaps. This action of the bile is apparently one of much importance to nutrition. When the secretion of bile is checked or diminished the absorption of fat from the intestine may suffer materially, even though there be a free secretion of pancreatic juice.

The object of the fat-splitting process which occurs in the course of intestinal digestion is obviously to facilitate or render possible the absorption and utilisation of the fat. Where both pancreatic juice and the bile are deficient, the splitting of fats and their absorption are materially reduced. It should not be supposed, however, that the loss of these digestive juices causes an entire cessation of the fat-splitting process. The splitting of fats into glycerine and the fatty acids takes place energetically in the lower part of the small intestine under the influence of organisms of the colon bacillus group. I have known the fæces under these conditions to contain a large proportion of fatty acids. The absorption of these acids is, however, greatly impaired. Of course, the

lower the melting-point of the fat employed as food the more complete will be the absorption. Thus olein is more rapidly utilised by the organism than palmitin or stearin.

What becomes of the fatty acids and soaps absorbed from the intestine? They pass almost exclusively into the lacteals and not into the mesenteric vessels and portal circulation. But they do not enter the lacteals as fatty acids. In their passage through the wall of the intestine a highly interesting synthesis takes place by which the fatty acids become converted into neutral fats. Thus Munk fed dogs for a time exclusively on fatty acids, but the lacteals were found to contain from 80 to 90 per cent. of neutral fat, and only 10 to 20 per cent. of fatty acids. In order that this conversion into neutral fat should occur a certain amount of glycerine is necessary. When free fatty acids are administered the glycerine is probably furnished by the cells forming the intestinal wall. When neutral fats are split in the intestine the glycerine yielded by the decomposition is absorbed in company with the fatty acids and soaps, and probably suffices for the subsequent synthesis. This useful synthesis is another example of the numerous syntheses performed by the body cells, and, like some of those of which I spoke in the first lecture, this one protects the organism against substances capable of acting injuriously upon the body. These substances in this instance are the free fatty acids.

I have already mentioned that the caloric value of the fats is very high, one gramme of fat yielding nine and five-tenths large calories gross. The yield of energy from the fats is thus more than twice as great as that derived from proteids or carbohydrates. This important peculiarity of the fats depends upon their chemical structure, which, as you will remember, is characterised by the presence of sixteen or eighteen atoms of carbon in a molecule of fatty acid, with only two atoms of oxygen in the molecule. Owing to this very low oxygen content a large quantity of oxygen is required for the conversion of the molecule of a fatty acid into the ultimate products of combustion, carbonic acid and water. In the course of this combustion there is consequently a greater yield of energy than if a smaller amount of oxygen were required to bring about the formation of the final products, carbonic acid and water. Human beings instinctively make use of the high caloric value of fat where a

great production of heat is required physiologically, as in the case of persons living in very cold climates. Such persons crave fats, eat them in large amount, and utilise them readily. On the other hand, persons living in tropical climates have an aversion to fat, which is based upon the relatively small caloric needs of the body, which radiates comparatively little heat.

In conditions of health, and also in disease, the fats are capable of replacing the carbohydrates to a considerable extent, or indeed exclusively for short periods of time. We often make use of this capacity of the fats to replace carbohydrates in cases of dyspepsia where the carbohydrates are only imperfectly digested and give rise to symptoms. We also employ the fats to replace partly the carbohydrates in diabetics who are unable to consume sugars normally in the organism. You remember that 100 grams of fat yields 950 gross calories. If now we should increase the quantity of fat to 200 grams, this would yield 1,900 gross calories. As a man of average weight requires less than 3,000 gross calories in twenty-four hours, you see how large a proportion of the caloric needs of the body can be supplied through a not immoderate increase in the fats of the food. You can also readily calculate how considerable a reduction of carbohydrate food is permissible under these circumstances.

Like carbohydrates the fats are capable of saving an excessive waste of proteid material; that is to say, the waste of proteids can be minimised by the administration and utilisation of considerable amounts of fats or carbohydrate material. In wasting diseases, with an excessive loss of proteid, as in phthisis or marasmus, from any cause, the fats may be used in abundance, since their utilisation is commonly less impaired than that of the carbohydrates. One reason for this is the readiness with which the fats are digested and absorbed, even when there is some derangement of gastric and intestinal digestion. This property renders the fats exceedingly useful in most chronic diseases of the gastro-enteric tract.

There is one effect arising from the use of fats which it is important for you to recognise. This is their action in facilitating the absorption from the intestine of the salts of calcium and magnesium. These salts are not very readily absorbed, owing to their slight solubility in the digestive juices. The presence of fatty acids in abundance favours

the formation of soaps of calcium and magnesium, which are much more readily taken up by the intestinal epithelium. It is especially important that the calcium and magnesium salts should be normally absorbed during the periods of infancy and childhood, when the skeleton is growing rapidly. The absence of a sufficient quantity of fat helps to deprive the skeleton of its normal supply of calcium and magnesium salts, and is, perhaps, one of the factors in the production of rickets.

The use of an abundance of fat in the food favours its accumulation in the body, and especially in the adipose tissues, where the surplus of fat over and above that burned for the maintenance of animal heat is stored.

The reason for the ready accumulation of fat in the body lies in the peculiarities of chemical constitution, already mentioned, which render fatty substances especially difficult to oxidise. Proteids and carbohydrates are readily oxidised and decomposed into the final non-nitrogenous products of combustion, carbon dioxide and water. The fats thus contrast sharply with these two great classes of food-stuffs, and this difference explains the unique position of the fats as stores of potential energy. We shall see that it is not clear whether fat is formed in the body from proteids, and that in any event the amount derived from this source must be very small. The stored fat must, therefore, come from the carbohydrates or the ingested fats, or from both sources. Of these two sources the ingested fat is probably the more important in the case of the human animal. This emphasises the importance of looking carefully after the fat absorption of our patients who suffer from impaired storage of fat—that is to say, are excessively lean. On the other hand it indicates the necessity of withdrawing fats largely from the dietary of those who are corpulent.

Whether an abundance of fat in the organism exerts any definite effect upon the constitution of the nervous system is uncertain. The nervous system contains large quantities of the bodies called *lecithins*, which may be loosely characterised as phosphorised fats, and it is possible that a deprivation of fat may result under some circumstances in a diminished formation of lecithins. I was unable, however, to find any evidence of a diminished lecithin content of the nervous system after prolonged fat starvation in pigs. It is customary to use fat in abundance in cases of multiple

neuritis, where the peripheral nerve fibres have been extensively damaged. In such cases the oily substance known as myeline which surrounds the axis-cylinders of the nerve fibres is extensively broken up, and it has been thought by some writers that the fat of the food is capable in some way of replacing this myeline. While it is very doubtful if this be the case, it is probable that the free use of fat is helpful in favouring the recovery of persons suffering from multiple neuritis. It is, however, not unlikely that this benefit arises from the effect upon general nutrition, rather than from any specific action on the nervous system.

One other use of fat as a food remains to be mentioned. I mean the influence of fat in overcoming constipation. You know that normally the fæces contain a considerable proportion of fat. Usually 10 or 15 per cent. of the dried substance consists of neutral fat, fatty acids, and soaps which have not been absorbed. This loss of fat in the fæces is in striking contrast to the behaviour of the soluble carbohydrates and proteids, which are found only in very small quantities or not at all. You will thus see that the fats form an important portion of the bulk of the fæcal material, and thus aid in the prevention of constipation. If the fats be markedly reduced in the food, either of adults or children, there is always an immediate tendency to constipation. On the other hand an increase in the proportion of fats in the food often tends to overcome any slight inclination to constipation. The knowledge of this fact will often aid you in the treatment of constipation, especially in children. During the first six months the milk fat in an infant's food should be increased as high as 3 per cent. By the end of the first year it should be raised to 4 or 4·5 per cent. It is ordinarily unadvisable to increase the proportion of milk fat beyond this point, and this usually suffices to prevent the occurrence of constipation.

I have now spoken to you in some detail of the chief indications for the employment of fat as a food. It is proper that I should say a word as to the various contra-indications to the use of full quantities of fat. In the first place, in the various acute catarrhal inflammations of the gastro-enteric tract, both in children and in adults, the use of fats in considerable quantities is objectionable. It is objectionable because the fats are not absorbed under these conditions, and are probably only imperfectly digested.

Their presence in the intestine in such large amounts is a mechanical hindrance to the absorption of proteid and favours putrefaction. It is also objectionable because of the irritant action of the lower fatty acids that may be liberated. There is one particular class of disturbances of digestion in which the use of fats should always be restricted, namely, conditions which shut off the bile or pancreatic juice, or both, from the intestine. Thus, whenever stools are acholic, it is objectionable to give full quantities of fat in the diet. The amount which may be allowed will differ in different cases. The best indication as to how much fat should be allowed is to be found in the quantity of fat contained in the stools. A considerable excess of fat in the stools, say 25 or 30 per cent. of the dried substance, may be permitted, but it is undesirable to permit a continuous and very large loss, such as 50 or 60 per cent. The proportion of fat in the stools can always be reduced by diminishing the quantity of fatty food. In all cases of jaundice it is best not to permit the patient to take milk containing more than 1 or $1\frac{1}{2}$ per cent. of milk fat. This is about the proportion found in ordinary skimmed milk.

It is by no means uncommon to observe regurgitation of food in children from the use of an excessive amount of milk fat. In other cases a moderate amount of fat gives rise to the same effects. If we reduce the milk fats to 1 or 2 per cent. temporarily, this regurgitation can usually be quickly checked. There are also many patients with chronic gastritis who do badly on milk containing the ordinary amount of fat. It is not exceptional for such patients to complain of nausea, which they attribute to the milk. When skimmed milk is substituted the nausea disappears.

Whether the continuous use of fat as a food is absolutely essential for the maintenance of nutrition and normal growth is not quite clear. In certain animals with vigorous digestions it is possible to replace fats wholly by means of carbohydrates for many months at a time. This can be done in the case of young pigs without producing any distinctly deleterious effects. It is very doubtful, however, if fat can be excluded from the human dietary without producing digestive and nutritional derangements. While the carbohydrates are capable of replacing the fats to a considerable extent, the quantity of carbohydrate food which is necessary to effect this replacement is so great that it soon leads to fermentative dyspepsia and its consequences. Hence the

use of such large quantities of carbohydrates has to be discontinued in the course of time, and fats are required to meet the caloric requirements of the body. The fats can also be replaced to a considerable extent by a large increase in proteid food, but the increase required for this purpose soon impairs digestion by favouring putrefactive excesses in the intestine. At least a moderate quantity of fat is thus essential to the dietary of a normal human being.

Certain effects of prolonged deprivation of fat are of considerable pathological interest. If a young pig be almost wholly deprived of fat for a considerable period of time, the adipose tissue in various parts of the body undergoes a peculiar form of atrophy. This atrophy can, however, be prevented if a large excess of carbohydrate food be administered during the period of fat starvation. The changes which occur in well-marked examples of fat starvation consist chiefly in a great shrinkage in the size of the fat cells, from which all the fat is in time removed.

The spaces between the shrunken fat cells are filled with a peculiar serous fluid, which also partly replaces the fat which has been removed from the fat cells. In the ordinary forms of fat atrophy such as you have noticed in most cases of wasting disease the layer of fat beneath the skin grows gradually thinner, but retains the yellow colour and consistence of normal fat, or a colour and consistence closely resembling this. In the condition which I am describing to you the gross appearances are very different and highly characteristic. On section through the adipose layer it is noticeable that the fat has been replaced by a semi-solid gelatinous somewhat greyish-looking layer. This material looks œdematous, but no fluid can be expressed from it. The condition is one which you will see occasionally at autopsy in certain cases of wasting disease, and especially in chronic phthisis. The completely transformed gelatinous layer is seen especially about the heart and about the kidneys, more rarely in the subcutaneous tissues. This striking type of fat atrophy is known as serous atrophy. It doubtless arises in the human subject, as in the experimental cases which I have studied, from a prolonged deprivation of fat—a deprivation not sufficiently compensated by the utilisation of carbohydrate to prevent the complete removal of fat from the adipose tissues, and its replacement through the serous material which I have mentioned.

Another phenomenon of much interest in connection

with the metabolism of the fats is the excessive accumulation of fats which occurs in some kinds of cells under pathological conditions. It is a question of importance in pathology whether such an accumulation of fat is due to an infiltration of fat, or whether it depends upon an actual transformation of the proteids of the cell protoplasm, in which case the accumulation would be the evidence of a degeneration rather than an infiltration. This question is still under discussion. It is claimed by some observers that fatty degeneration does not occur, and that the excessive fat observed in the cells of the liver and kidney in disease is carried to these cells from the adipose tissue. Certain experiments seem to give support to this view. For example, it is claimed that the excessive accumulation of fat which occurs in the liver after phosphorus poisoning in dogs does not take place if the dogs be starved previous to the poisoning to such a point that the fat in the various adipose depôts is exhausted. On the other hand, if a dog whose adipose deposits have been exhausted by starvation be then fed upon a foreign fat with a different melting-point from that of dog-fat, there is an accumulation of this foreign variety of fat under the skin and elsewhere. If now the dog thus prepared be poisoned with phosphorus, the foreign fat is found on autopsy to have been deposited in considerable quantity in the cells of the liver, giving rise to histological appearances like those often described in fatty degeneration. There can be no doubt that infiltration of fat from distant fat depôts is a very common process in conditions of disease. It is by no means clear, however, that all pathological accumulations of fat in the cells of the liver and elsewhere are dependent upon infiltration. I shall point out to you in the next lecture that the proteids entering into the constitution of the cell protoplasm are capable of yielding a certain definite and very considerable proportion of carbohydrate material. Now we know that the organism possesses the power of converting carbohydrate material into fat through a process of synthesis. It seems possible, and even likely, that under some conditions of disease this conversion of carbohydrates into fat continues, notwithstanding damage to the cell protoplasm. But it cannot be said that this origin of fat from proteid has been actually established, and it must indeed be admitted that the best experimental observations have yielded no evidence in support of such an origin.

In thinking about the accumulation of excessive quantities of fat in the liver cells and other cells it is important for you to realise that such an accumulation in moderate degree is an entirely normal process. The fat which accumulates in the liver after a meal rich in fatty substances is detained there by the liver cells for the purpose of being burned. I am inclined to believe that the burning of fats, that is, their utilisation for the production of heat, goes on more energetically in the cells of the liver than anywhere else in the body, and I believe that this energetic oxidation of fats is one of the reasons why the temperature of the liver is distinctly higher than the temperature of other organs in conditions of health. If now we suppose that in the various conditions of disease where the cells of the liver are damaged by the action of certain poisons the liver cells have lost their capacity to oxidise and break up fats, while they still retain the ability to accumulate fat brought to them in the blood, we can see why there should be under these circumstances an excessive accumulation of fat in the liver. Such an accumulation of fat does not imply that the liver cells have entirely lost the function of burning fat nor the function of utilising other kinds of food materials. I have already told you that the fats of all the different foodstuffs are the most difficult to burn, and it is not singular that when a failure begins in the oxidative functions of the liver cells this failure should be first noticed in the defective capacity for utilising fats. This view is entirely in harmony with the fact that extreme degrees of fatty change in the liver cells are consistent with the maintenance of various important functions of the liver.

A question of much physiological and pathological interest is whether fat is ever capable of yielding sugar in the course of metabolism. Many experiments have been made to discover whether fat is a producer of glycogen. The introduction of large quantities of fat with the food and the direct injection of fat into the circulation have never been found to increase the glycogen content of the liver. Moreover the feeding of large amounts of fat to diabetic patients has never been observed to increase the output of sugar.

In consequence of these negative results the view has come to be generally accepted that the combustion of fat in the organism does not yield carbohydrate. This conclusion appears to hold good for conditions of health, but it is

doubtful if it is true of certain pathological states. Thus Hartogh and Schumm, in a paper recently published from Rumpf's laboratory, bring forward observations which, if accurate, strongly support the view that sugar may be derived from fat. These workers found it possible to induce in dogs a state of phlorhizin diabetes in which so much sugar was excreted in proportion to the nitrogen eliminated that a portion of this sugar could have been derived neither from the proteids of the body nor from the stored carbohydrates of the organism. The experimental conditions appear to have been such as to compel us to attribute the great excretion of sugar either to the origin of sugar from fat or to the synthesis of sugar from carbon-holding decomposition products of the proteid molecule.[1] The latter view must, however, be regarded as very unlikely.

Besides these cases of diabetes from phlorhizin there are instances of human diabetes in which the quantity of sugar excreted is so great that a portion of it must be attributed to the pathological metabolism of fat. The diabetic patients of whom this is true are victims of the severest form of diabetes, and are usually in the terminal period at the time of this great excretion of sugar. I shall have more to say of the origin of sugar from fat when we come to the discussion of diabetes. In the meantime do not imagine that we are accurately informed as to the precise conditions under which fat yields sugar to the organism.

In the few minutes which remain I wish to tell you something about the different forms in which fat is employed as a food. The most important of the fats in general use is that which is contained in milk. It might, perhaps, appear to you at first sight a matter of indifference whether you give fat in the form of cream or butter, but in reality this is not the case. One meets with many dyspeptic patients who are able to take butter in abundance, but who do badly on the use of cream. Nausea or a sense of distress after the use of cream in considerable amount is by no means uncommon. Probably the chief reason for this difference in the tolerance of the two forms of fat is that in cream the fat is present in the form of globules of neutral fat which have to

[1] Results recently obtained in my laboratory are not in accord with those obtained by Hartogh and Schumm, and Dr. Lusk tells me that in his experiments he has failed to obtain the very high proportion of sugar to nitrogen which these writers report.

be split into glycerine and fatty acids to prepare the fat for absorption. Butter, on the other hand, contains about 7 per cent. of fatty acids (butyric, caproic, &c.). In other words butter is already partially prepared for absorption. The absorption of butter-fat is therefore apt to be more rapid, and perhaps more complete, than the absorption of cream-fat. This is especially true in pathological states of digestion. In normal persons there may be no apparent difference in the digestibility and absorption of the two kinds of fats. In cases where it is important for us to administer large amounts of fat, but where the digestive powers are weaker than normal, it may be advisable to make use of an emulsion. The fat emulsions vary a good deal as to the fineness of the fat globules. The smaller the globules, the greater is the likelihood of rapid absorption, owing to the greater readiness with which the process of fat-splitting is carried on.

A small quantity of free fatty acids is found in cod-liver oil and in many of the vegetable oils, such as olive oil. The preparation known as Lipanin is made from olive oil containing about 6 per cent. of free oleic acid. It is questionable whether cod-liver oil possesses any therapeutic properties unconnected with its low melting-point and its small percentage of free fatty acids.

It has often been observed that patients who have a dislike for fatty food are able to take more of it when alcohol in some form is administered at the same meal. The use of small quantities of alcohol may thus be helpful in favouring the intake of an important class of food. Cases will come under your observation in which you can safely recommend small quantities of alcohol for this purpose, but please remember that this is only permissible when gastritis is not present, and where there is no indication that the alcohol acts detrimentally on the stomach. It has been thought by some that the use of alcohol simultaneously with fats favours the absorption of fat, but there is experimental evidence that this is an erroneous notion. Many persons look upon chocolate as a highly nutritive form of fat, and recommend its use. The fat contained in chocolate is cocoa butter, a substance agreeable to the taste, but with a much higher melting-point than ordinary fats. In normal individuals the use of small quantities of chocolate is not objectionable, but in most disturbances of gastric or intestinal digestion it is probably best to forbid its use altogether.

Attempts have occasionally been made to employ glycerine as food, but there is no justification for this whatsoever, since glycerine acts as an irritant, and is very apt to set up diarrhœa. The body cells furnish a sufficient quantity of glycerine to effect the necessary synthesis of fatty acids into neutral fat.

Attempts have frequently been made to improve the nutrition of patients in wasting disease by means of inunctions of cod-liver oil or other fats. These efforts have met with little success. The skin appears to take up such small amounts of fat that it is hardly worth while to make use of so disagreeable a method. Rectal injections containing fats have also met with little success, as the quantity of fat absorbed from the nutrient enemas is very small. A far more satisfactory method of administering fat is by subcutaneous injection. The introduction of olive oil under the skin is followed by the gradual removal of the fat from the point of entry and its utilisation by the organism. It is stated that none of the fat introduced finds its way into the urine. The use of fat in this way may to a considerable extent save the nitrogen of the body in cases where only a limited and insufficient quantity of food can be taken by mouth. From 50 to 100 c.c. of olive oil may be introduced under the skin in the course of twenty-four hours. You can see that the use of such considerable quantities of fat enables one to place at least 500 calories at the disposal of the organism. If the injection be made very slowly under aseptic precautions, there are no ill results. If the injection be made more rapidly than at the rate of 2 c.c. per minute, it may give rise to considerable pain. The injection must be made where the folds of the skin are loose, and different places must be selected from day to day. The procedure has been carried on daily for weeks without giving rise to unpleasant consequences, but if you employ this method it is essential to guard most rigidly against infection.

Probably the best results from the subcutaneous injection of fats are to be obtained in connection with nutrient rectal enemata. We shall see that the absorption of proteids and carbohydrates from enemata is satisfactory, while the absorption of fat is very slight. Hence the subcutaneous injection of fat is an admirable supplementary measure to the use of nutritive enemata.

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LECTURE III

THE CHIEF FOOD-STUFFS AND THEIR FATE IN THE BODY IN HEALTH AND IN DISEASE.—THE PROTEIDS

Elements entering into proteid molecule—Replacement of cell waste by proteids—Large size of proteid molecule—Cleavage products—Hexo-bases, histidin, lysin, argenin—Protamins—Amido-acids: leucin, tyrosin, aspartic acid—Ammonia: its origin during metabolism—Melanins—General reactions of proteids—Biuret reaction—Millon's reaction—Adamkiewicz's reaction—Sulphur, phosphorus, and iron in the proteid molecule—Classification—Gastric digestion of proteids—Intestinal digestion of proteids—Absorption of proteids—Albumosuria—Albumoses and peptones—Caloric value of proteids—Forms of proteid food—Animal and vegetable proteids—Milk—Peculiarities of milk as a food—Influence on intestinal putrefaction—Influence on excretion of uric acid—Dietetic uses of milk in disease—Disadvantages of milk—Peptonisation of milk—Sterilisation and Pasteurisation or partial sterilisation—Preservation of milk by formalin—Toxic effects of milk—Cheese—Skimmed milk—Buttermilk—Fermented milk-foods: kumyss and matzoon—Condensed milk—Caseon—Whey—Eggs—Meats—Meat extractives—Large percentage of ammonia derived from meat—Beef extracts—Somatose—Gelatin—Importance of proper cooking.

This morning we have to consider the most important and complex variety of food-stuffs—namely, the proteids. The proteids are characterised by the fact that they contain nitrogen in addition to carbon, hydrogen, and oxygen, which three elements we have seen to be the constituents of the carbohydrates and fats. Probably all proteids contain also a variable but small proportion of sulphur and a still smaller amount of iron. Many proteid substances contain phosphorus.

The carbon of the proteid molecule exists partly in combinations of the fatty acid series, partly in aromatic bodies. Much the greater part of the carbon is in union with nitrogen. The nitrogen of proteid appears to exist largely in amido (NH_2) groups. A portion of the nitrogen (usually less than

20 per cent. of the total nitrogen) is readily split off as ammonia, a larger percentage is separable as basic diamido-acids, while the greater part of the nitrogen is obtainable as monamido-acids. The sulphur of the proteid molecule exists in two forms. One of these is a loose combination, comparable to the nitrogen of ammonia in the readiness with which it is split off. The remaining sulphur can only be detected on complete combustion of the proteid molecule when it appears as sulphuric acid. We are ignorant of the state in which this portion of the sulphur exists in living protoplasm. Neither do we know in what form iron is present.

The proteids hold a unique position as food-stuffs. Like the carbohydrates and fats, they furnish the organism with potential energy for the development of heat and work, but, unlike these, they are capable of replacing the nitrogenous waste of the cells of the organism generally. The uninterrupted decomposition of the proteid materials of the cell is an essential condition for the maintenance of life. This continuous waste, which goes on even during starvation, must be replaced, and the only kind of food capable of replacing the nitrogen of the cell is the proteid food. It will, perhaps, help you to think of the processes of combustion in the body as resembling a fire in which the kindlings may be compared with the proteids. The proteids in the body-cells and the kindlings in the fire resemble one another in being easily burned and in being essential to initiate the combustion of other substances. If we add coals or other less combustible material to the fire, it is readily burned in the presence of the burning kindlings. Similarly, carbohydrates and fats are readily burned in the course of the oxidative processes which constantly go on in an energetic way in the proteid constituents of the cells. Essentially the same idea may be stated in a somewhat different form. The chemical affinities of the cells are strongest for the proteids, less strong for the carbohydrates, and weakest for the fats. The proteids are the most readily burned food-stuffs; the fats are the least readily burned.

It is, of course, by virtue of the nitrogen contained in the proteid molecule that the derivatives of the proteid food are capable of replacing the nitrogenous waste of the cell.

One of the most remarkable features of the proteid molecule is its large size. I cannot do better than to call

your attention to the composition of the molecule of hæmoglobin as an illustration of this fact. The hæmoglobin molecule may be represented as follows :—

$$C_{712}H_{1130}N_{214}O_{245}FeS_2.$$

I have chosen the composition of hæmoglobin as an illustration of the size and complexity of the proteid molecule because this is one of the animal proteids which occur in crystalline form, and hence in a pure form. In the case of other proteid substances it has not been possible until quite recently to induce crystallisation, and hence investigators have only begun to succeed in establishing the composition of such proteids. Even in the case of hæmoglobin the analytical results obtained by different chemists are not precisely the same for hæmoglobin from the same species of animal. We may, however, assume that the empirical formula which I have given you is approximately correct. We know that hæmoglobin breaks up into an iron-containing substance called hæmatin, and into a proteid belonging to the class called histones. Now the composition of hæmatin is definitely known, and is as follows : $C_{32}H_{32}N_4O_4Fe$. If, therefore, we subtract the atoms of the molecule of hæmatin from the atoms of the molecule of hæmoglobin, it gives us the composition of the proteid histone, known as globin, which is as follows :—

$$C_{680}H_{1098}N_{210}S_2O_{241}.$$

The large size of the proteid molecule is closely connected with some of the most important physical and chemical attributes of the proteids. It is responsible, for example, for the great difficulty with which diffusion takes place through animal membranes, and helps us to understand why it is that the proteids of the blood plasma are held within the blood vessels, while the salts and the material of smaller molecules readily diffuse through the vessel walls. The ' colloid ' nature of the proteids is thus dependent on the large size of the proteid molecule.

On considering the large numbers of atoms which go to make up a molecule of proteid substance, it naturally occurs to one that so complex a molecule must be capable of breaking down into a variety of smaller molecules, or, in other words, that the cleavage of proteids must yield

numerous and very different products. This is actually the case. The kind of product derived from the splitting of the proteid molecule depends somewhat on the nature of the proteid itself and in part upon the conditions under which the cleavage occurs. For instance, the proteids are decomposed in the animal body during tryptic digestion in the intestine, during putrefaction, and in the course of metabolism in the cells and outside the body through the action of acids or of alkalis. While the products which result are somewhat different according to the conditions attending the cleavage, there is nevertheless a resemblance in the derivatives which arise under these different circumstances, and this similarity in products is the result of the inherent chemical constitution of the proteid.

I shall now enumerate the chief products of cleavage of the proteid molecule under tryptic digestion, referring briefly to some of the leading characteristics of these cleavage products. The products arising through bacterial activity will be mentioned in connection with intestinal putrefaction. For a detailed account of the products of proteid cleavage I must refer you to the works on physiological chemistry.

It is convenient to divide the products of the tryptic cleavage of proteids into those which contain nitrogen and those which do not. Of the nitrogenous products the most important are the bodies known as lysin, histidin, and argenin, the amido-acids (leucin, tyrosin, and aspartic acid), and ammonia. The bodies which are called histidin, lysin, and argenin are represented respectively by the following formulæ :—

$$C_6H_9N_3O_2,\ C_6H_{14}N_2O_2,\ \text{and}\ C_6H_{14}N_4O_2.$$

I should like you to observe that these three bodies resemble one another in that each molecule contains six atoms of carbon. Owing to this fact, and to the circumstance that these substances possess basic properties, they are known as hexo-bases. I may here call your attention to a certain resemblance between these bodies and the hexoses or sugars containing six carbon atoms in the molecule. It does not require a great flight of the imagination to conceive of the transformation of the hexo-bases lysin and argenin into the sugars. It would be necessary, of course, in effecting such a transformation to remove the nitrogen from the

hexo-bases entirely, to reduce somewhat the hydrogen in the case of lysin and argenin, and to increase the content of oxygen, since, as you remember, the hexoses contain six atoms of oxygen to the molecule, while these hexo-bases of which we are speaking contain only two atoms to the molecule. It is thought by some of the most distinguished physiological chemists that in the course of metabolism proteids are capable of yielding carbohydrate material, such as glucose, through a transformation of the hexo-bases in some such way as I have indicated to you. Whether this is the precise mode in which the proteids yield carbohydrate material is, of course, far from being demonstrated. There is no question, however, about the fact that proteids are capable of splitting up in the course of metabolism in such a manner as to yield sugar. This fact is clearly demonstrated by the behaviour of animals which have been rendered diabetic through the extirpation of the pancreas. As I shall explain to you with greater detail in the lecture upon diabetes, the removal of the entire pancreas in dogs is followed by the appearance of large quantities of sugar in the urine, and in the case of animals that are fasting. This sugar is present in a proportion which bears a fixed relation to the nitrogen found in the urine. This fact was first demonstrated by your professor of physiology (Dr. Lusk). The excretion of sugar occurs under such conditions that it is quite clear the sugar can be derived only from the breaking down of the proteid molecules of the cells. It is certainly interesting to think of the possibility that this sugar arises from the hexo-bases—histidin, lysin, and argenin.

Under the influence of tryptic digestion the yield of hexo-bases is small. It is not without interest to stop for a moment to consider the origin of the hexo-bases—histidin, lysin, and argenin—from the proteid molecule. It is, of course, conceivable that these bodies might result from a cleavage of the proteid without intermediate more complex antecedents. As a matter of fact, however, it has been recently determined that the hexo-bases—histidin, lysin, and argenin—can be split off from a more complex proteid derivative by means of a hydrolytic process. Several allied bodies are capable of yielding histidin, lysin, and argenin in this way. Such bodies have been given the general name of *protamins*. It is thought that the protamins constitute

the real chemical nucleus of the proteid molecule, and there is considerable evidence that this is the case. A particular protamin, which has been isolated by Kossel from the eggs of the salmon, is known as salmin. Salmin was found to have the following composition: $C_{30}H_{57}N_{17}O_6$. The protamin salmin yields on decomposition one molecule of histidin, one molecule of lysin, and three molecules of argenin for each molecule of salmin. It is not unlikely that the hexo-bases arise in a similar way in the cellular metabolism of the higher animals. The nature of the carbohydrate moiety of the proteid molecule is, however, still the subject of discussion.

Possibly you have gained the impression that all proteids are capable of yielding sugars of the hexo-type—that is, containing six atoms of carbon. While this is true of mucins, and of various animal and vegetable albumins, it does not hold good for all proteids. Thus there are some proteids, like casein and vitellin, which have hitherto failed to yield any carbohydrate moiety whatever. There are also some proteids which yield carbohydrate groups united to NH_3 groups—amido-hexoses these bodies are called. Then, again, some proteids, like the nucleo-proteids of the pancreas and liver, yield, not hexoses, but pentoses—that is, sugar containing five carbon atoms instead of six. In diabetes the urine sometimes contains sugar of the pentose class; a fact of considerable interest in connection with what I have just said about the pentoses yielded by the nucleo-proteids.

The second group of nitrogenous products of proteid cleavage is made up of the amido-acids—that is, acids of the hydrocarbon or fatty-acid series—in which one hydrogen atom has been replaced by the amido-group (NH_2), as, for instance, in the following examples:—

(1) Leucin or *a*-amido-isobutylacetic acid is $C_6H_{13}NO_2$, or $(CH_3)_2$, CH, CH_2, $CH(NH_2)$, COOH. In tryptic digestion the yield of leucin is large.

Leucin was formerly supposed to be amido-caproic acid.

(2) Tyrosin or *p*-oxyphenyl-amido-propionic acid is $C_9H_{11}NO_3$, or $HO.C_6H_4.C_2H_3(NH_2).COOH$. The tryptic yield of tyrosin is much less than the yield of leucin.

(3) Aspartic acid or amido-succinic acid is $C_4H_7NO_4$, or $C_2H_3(NH_2).(COOH)_2$. The yield of this amido-acid from proteid is very much smaller than the yield of leucin.

The chief amido-acids are leucin, tyrosin, and aspartic acid. Their chemical constitution is indicated in the formulas to which I have just called your attention. Aspartic acid is of comparatively little interest in the human organism, but is highly important in the metabolism of plants, which probably build up their proteids by means of synthetic processes in which aspartic acid plays a prominent part. Leucin and tyrosin differ in the very important feature that leucin is a fatty acid derivative, whereas tyrosin is a derivative both of the hydrocarbon and the aromatic series. Leucin appears to be rather readily burned in the organism. Tyrosin is also broken up by oxidation, both during metabolism and through the action of putrefactive bacteria, but tyrosin cannot be oxidised to the point where its benzol ring is broken up. Instead of breaking down in the body the aromatic nucleus becomes converted by oxidation into phenol or carbolic acid, and finds its way as a phenol compound into the urine. Where the oxidation processes of the body are greatly reduced—as in some cases of liver disease—the leucin and tyrosin formed in the intestine in the course of proteid digestion are not oxidised as in health. In consequence of this leucin and tyrosin sometimes make their appearance in the urine. Whether these amido-acids are ever derived from the breaking down of the proteids belonging to the cell protoplasm of the body is a question which cannot be answered at present. Leucin and tyrosin and aspartic acid are simpler substances than the hexo-bases of which I just spoke to you. They probably are the source of very little chemical energy in the body, and cannot at last be regarded as possessing more than a very low food value. The hexo-bases, on the contrary, are probably most important sources of chemical energy.

One of the most important products of the cleavage of the proteid molecule is ammonia. The formation of ammonia occurs as one of the end products of tryptic digestion, but only in small amount in the course of normal human digestion. A far larger proportion of ammonia results from the cleavage of proteids in the course of normal metabolism.

This metabolic ammonia has two entirely distinct sources. One of these is the life activities of the cells of the organism generally. This mode of origin is entirely independent of the food supply. Cut off the food supply wholly and the ammonia continues to be produced, to be converted under

normal circumstances into urea. An excellent proof that ammonia is still formed by the cells in starvation is to be seen in the results of administering large doses of a mineral acid to an omnivorous or carnivorous animal. The urine under these circumstances contains a large amount of ammonia united to the acid which has been neutralised to protect the organism.

The second metabolic source of ammonia is proteid food, and especially the proteids of muscle. A few minutes ago I spoke of the ammonia derived from tryptic digestion, but this is not the source of ammonia which I now have in mind. I refer to ammonia which is split off from the muscle proteids of food by cells in the wall of the intestine. The high percentage of ammonia in the portal vein after a meal of meat depends on this cleavage. This ammonia adds greatly to the ability of an animal to neutralise acids, since it reinforces that derived from the cells generally.

These facts enable us to explain why herbivorous animals, with little ammonia at their disposal, succumb readily to poisoning by acid, while carnivorous animals are far more resistent.

I have already told you something about the fate of ammonia when speaking of the synthetic processes which protect the organism against the action of certain poisons. You will remember that I mentioned to you the conversion of ammonia into urea through synthesis with carbonic acid. One can form some estimate of the very considerable yield of ammonia which must occur in the course of metabolism in order to give rise to so large a quantity of urea as is excreted daily through the kidneys, although I do not wish you to infer that all the urea excreted is derived from this one source.

It may perhaps be not out of place to mention here the fact that various proteid substances are capable of yielding nitrogen-containing bodies which have a dark colour and possess the characters of melanins. These melanins have a distinct pathological interest, since they are formed in considerable quantities in certain pigmented tumours, as, for example, in melanosarcoma. It is easy to obtain melanin-like pigments through the action of sulphuric acid upon a number of different proteid substances. The different melanins, though closely allied, present certain variations in composition. As a class the melanins are characterised by

a rather high content of carbon, a relatively low percentage of nitrogen, and a variable but generally high proportion of sulphur. The absence of iron from most melanins has led to the belief that they do not originate from the blood pigment, while the presence of sulphur suggests their origin from proteid material.

I do not wish you to imagine that I have given you an adequate idea of the cleavage products of the proteids. I have mentioned only some of the more important substances formed in the course of tryptic digestion and during metabolism.

Physiologists as yet possess no satisfactory knowledge of the manner in which the different atoms are arranged in the proteid molecule. Certain general reactions of the proteids give us an indication of a variety of groups which they contain. Thus, as you know, all proteids give a pink or violet coloration when boiled with strong sodium hydrate, with the addition of a few drops of a very dilute solution of copper sulphate. This reaction, which is known as the biuret test, indicates that the proteids contain the biuret or urea group. Biuret is derived from urea by the removal of ammonia. Thus :

$$2CO\begin{matrix}NH_2\\ \\ NH_2\end{matrix} - NH_3 = C_2O_2N_3H_5.$$

Another important reaction which throws light on the nature of the proteid molecule is that known as Millon's reaction. This consists in a white precipitate soon changing to red, which results from the addition to a proteid of the nitrate of mercury in acid solution. The reaction is due to the presence of the aromatic nucleus contained in the proteid molecule, and the same reaction can be obtained from phenol, tyrosin, &c. The proteid molecule, however, contains more than one aromatic group. Thus the presence of an indol group, represented by the substances indol and skatol, appears to be indicated by what is known as the Adamkiewicz's reaction. This consists in a reddish-violet colour, which appears when a small amount of proteid substance is added to a mixture of concentrated sulphuric acid and glacial acetic acid.

Although much has been learned in recent years of the more intimate constitution of the proteids, we cannot conceal

from ourselves the fact that we are still a long distance from a knowledge of the arrangement of the atoms constituting the different varieties of proteid molecules.

I mentioned to you at the beginning of the hour that some of the proteids contain sulphur, phosphorus, and iron. It is important to call your attention to certain properties of proteid material which are closely connected with the possession of these elements. Iron is probably present in the protoplasm of all cells, and especially in that group of proteids known as nucleo-proteids, a group of substances capable of breaking down into an albuminous substance and nucleins. In what form the iron of the proteid molecule exists is not known, but it is clear that it must be present in some organic combination, and not in an inorganic form. This is shown by the fact that the iron of the cell does not give the ordinary reactions to iron which are readily obtained from its inorganic combinations. This masked iron, as it is sometimes called, is doubtless of the utmost importance in bringing about oxidative processes in the body, and any considerable diminution of the organic iron of the cell is probably attended by a diminution in the intensity of these processes. I shall speak to you again of iron in its relation to the animal organism when we come to review the inorganic food-stuffs. The presence of sulphur is characteristic of most proteid substances, and many such substances contain a high percentage of sulphur. This is the case, for instance, with a large group of bodies known as albumins. We do not know just how the sulphur in the proteid molecule is combined, but as I stated at the beginning of the hour it exists in two forms—one in loose union with the rest of the molecule, the other only recognisable on complete oxidation of proteid. In the course of the oxidative processes in the cells which attend the cleavage of the proteid molecule the loosely combined sulphur becomes largely oxidised to sulphuric acid. This acid combines with bases to form sulphates which are eliminated in the urine. Not all the sulphur leaves the body as sulphuric acid, a small proportion being excreted in the form of the organic substance known as taurin.

Phosphorus is a regular constituent of some proteids. The presence of phosphorus in the nuclei of the cells of the body seems to be closely connected with cellular functions of the utmost importance to the organism—*e.g.*

with the growth of the cell and with its capacity for reproduction. As in the case of sulphur and iron, we are ignorant of the precise form in which the phosphorus is held in the proteid molecule. It is clear, however, that in the course of the oxidations and cleavages that occur in the proteid the phosphorus becomes oxidised to phosphoric acid, and after uniting with bases is excreted by the urine as phosphates. In a general way we may say that there is a parallelism between the yield of phosphoric acid, of sulphuric acid, and of nitrogen in the course of the destructive metabolism of proteids. The more rapidly the cells of the body break down through physiological combustion, the larger is the amount of nitrogen found in the urine, and the larger also is the excretion of the sulphates and the phosphates. In wasting diseases in which there is excessive proteid decomposition the excretion of sulphates and phosphates keeps pace with the excretion of urea.

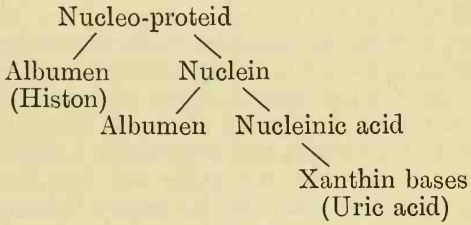
It is convenient to classify the proteids according as they contain phosphorus or not. In the large group of proteids and proteid derivatives which do not contain phosphorus we find the albumins, the globulins, hæmoglobin, acid and alkali products of the albumins, peptones and albumoses, mucins, amyloid substances, and certain proteids found in cartilage known as chondro-proteids. The substances grouped in this list are unlike in complexity, the albumins and globulins, for instance, being simpler in composition than the chondro-proteids or the mucins. Nevertheless it is desirable to group them as substances free from phosphorus.

The phosphorus-containing proteids can be divided into two groups, the nucleo-albumins and the nucleo-proteids. A good example of a nucleo-albumin is the casein of milk. The nucleo-albumins on being split up yield an albumin and phosphoric acid. You remember that casein contains phosphorus when I remind you that the urine of people who are put on a milk diet usually becomes strongly acid. This acidity is due in large measure to the presence in the urine of the acid sodium phosphate, which is more abundantly formed on a diet of phosphorus-containing proteids than on foods free from phosphorus.

The members of the second group of phosphorus-containing substances—namely, the nucleo-proteids—are characterised by the fact that they yield both nucleins and

albumins. The phosphorus-holding nucleins yield albumin and a nucleinic acid on further decomposition, the phosphorus belonging to the latter body. As the different nucleo-proteids have nucleins of different constitution, it is not surprising that there should be different nucleinic acids. Thus the nucleinic acid obtained by Mathews from herring sperm is represented by the formula $C_{40}H_{54}N_{14}O_{27}P_4$, while the acids derived from the sperm of other fishes, from yeast, and from other cells are represented by somewhat different formulæ.

The following scheme may help you to remember the constitution of the nucleo-proteid constituent of cells :—



A highly important characteristic of nucleinic acids is the fact that they yield the substances known as xanthin or protein bases.

I cannot stop to explain to you the stages through which the nucleinic acid derived from the nuclein may be converted into the various members of the group of xanthin bases. In a subsequent lecture I shall discuss this with you in detail. At present I ask you to remember the fact that uric acid is the best known, though perhaps not the most important, of the xanthin bases, and that it represents the last link in a series of changes which begin with the conversion of nucleinic acid into the closely allied basic substances adenin and guanin. I will ask you also to remember that substances rich in nuclein lead to the production of large amounts of uric acid. This is a circumstance of very considerable significance in the treatment of disease. Where we wish to avoid the formation of uric acid in excessive amounts we must be particular not to allow our patients to eat foods rich in nucleins. All tissues in which the nuclei are large in proportion to the cell bodies are rich in nuclein. The thymus gland, which is often eaten as a sweetbread, is an

example of this. Young meats have the same peculiarity. The story is told of a manufacturer of carpets that he encouraged his men to eat veal in order that he might recover large quantities of uric acid from their urine. The uric acid he utilised to make the beautiful dye known as murexid, which he employed in staining his fabrics. I cannot leave this subject without calling your attention to the fact that the two groups of phosphorus-containing proteids, the nucleo-albumins and the nucleo-proteids, are sharply contrasted as regards their influence on the formation of uric acid in the body. While the nucleo-proteids lead to the abundant formation and excretion of uric acid, the use of the nucleo-albumins, as represented by casein, leads to a marked reduction in the ordinary output of uric acid. The utility of milk in treating disorders characterised by an excess of uric acid in the urine is partly referable to this fact.

Besides the various types of proteids of which I have spoken there is a group of closely allied bodies to which the name albuminoids has been given. The keratins found in horny tissues like the nails and hair, the elastin found in elastic tissues, and the kollagens belonging to tendon and bone, and represented by gelatin, are examples of albuminoids. The albuminoid substances are made up of molecules of less complex structure than the true proteids. For example, it is inferred from certain general reactions that whereas egg albumin, which is a true proteid, contains at least three different aromatic groups, gelatin contains but one such group. Owing to the greater simplicity of the albuminoids these bodies are incapable of replacing the nitrogen lost through the waste of proteids in the cell substance. They cannot therefore take the place of proteid food. Gelatin is, however, capable of sparing proteid waste under some circumstances much as is done by fats and carbohydrates.

I will now ask your attention to certain processes connected with the digestion and absorption of proteid foodstuffs in the human organism. You know that the native proteids, such as egg albumin and casein, which we take with our food, undergo partial digestion in the stomach through the action of hydrochloric acid and a ferment of the gastric juice. Albumins are converted first into acid albumin, and, later, undergo transformation into albumoses, and to a much less extent into peptone. In cases where the hydrochloric

acid and the ferment of the gastric juice are deficient the formation of albumoses and peptone does not occur in the stomach. In such instances the work which should be performed by the stomach is done in the intestines through the action of the trypsin or proteolytic ferment of the pancreatic juice. Intestinal digestion appears to be capable of compensating wholly or largely for the failure of proteid digestion in the stomach. Even in health proteid digestion does not usually advance very far under the influence of hydrochloric acid and pepsin. Only a small portion of the native proteid becomes converted into peptone, which is the terminal product of normal proteid digestion. The absorption of proteids from the stomach also appears to be insignificant in amount.

The acid contents of the stomach on entering the duodenum give rise to a free secretion of the alkaline pancreatic juice. It has been shown conclusively that the hydrochloric acid of the gastric juice constitutes a most important physiological stimulus to the secretion of pancreatic juice containing an abundance of tryptic ferment. Under the influence of trypsin, in the alkaline medium of the pancreatic juice, there occurs an energetic conversion of the proteids and proteid derivatives which have come from the stomach into albumoses and peptone. Peptone, the last proteid product in the digestion of proteid, is readily absorbed from the walls of the intestines. The more rapidly the process of digestion goes on the more rapidly does the absorption of peptone occur. If digestion is slow, owing to an excess of proteid food or to a deficiency in the tryptic ferment of the pancreatic juice, the absorption of proteids is slow. In other words, there remains under these conditions a considerable amount of proteid material which is not rapidly converted into a form fitted for absorption. Moreover, even if much of the ingested proteid be converted into peptone the quantity fitted for absorption may be so considerable as to lead to some delay in being taken up by the intestinal epithelium. When this happens in consequence of an excessive proteid meal, other factors enter into the process of bringing about the proteid cleavage. The bacteria with which the intestine swarms act rapidly upon peptone and albumoses, breaking them down into simpler substances than those pertaining to tryptic digestion, such as tyrosin, indol, and phenol, and probably with an excessive yield of

leucin, ammonia, and other bodies. If the conditions of digestion are such that a considerable proportion of the proteid food is broken up into these products, the loss of potential energy to the body may be great, for, as I have already explained to you, the organism needs the complex proteid molecule to replace the constant proteid waste of cells. Peptones and albumoses furnish the necessary nitrogenous food material, but when peptone is cleft through bacterial action into leucin, tyrosin, &c., there is necessarily a distinct loss of proteid food material which may cause the body to lose nitrogen. But this loss of proteid from excessive proteolysis is by no means the only important effect of excessive bacterial activity. Some of the cleavage products of peptones and albumoses exert a distinct if not considerable toxic action, and this toxic action in some instances leads to pronounced pathological consequences. I shall have something to say to you on this subject when we discuss excessive intestinal putrefaction.

In health the absorption of proteid material from the intestine is excellent. Very little proteid finds its way into the fæces, and what there is appears to be derived largely from intestinal epithelium and the succus entericus. Albumoses and peptones are not found. Of course the fact that proteids are not found in the fæces except in small amount is not necessarily an indication that the proteids have been absorbed as such. It is conceivable that they may have been to a considerable extent broken up into the simpler products of proteolysis which I have already mentioned. Similarly the absence of carbohydrates in the fæces does not signify that these substances have been absorbed as such, for they may have been largely broken up through excessive fermentation.

The absorption of proteids does not occur to any considerable extent through the physical processes of filtration and osmosis, but must be regarded as arising through definite vital activities of the epithelial cells lining the intestine. The peptone which has been absorbed passes, not into the lymph-vessels, but almost exclusively into the blood-vessels. It is a remarkable fact, however, that the peptones absorbed are found in very small amounts in the mesenteric vein, and that they rapidly disappear from the circulation when injected into it. It is quite clear that certain cells of the body are capable of rapidly converting

peptone and albumoses into some other substance, perhaps serum albumin. It is still uncertain whether the disappearance of the peptones absorbed from the intestine is effected through the action of the epithelium of the intestine or through the activity of the lymphoid cells and the leucocytes which are present during the digestion in such large numbers in the intestinal walls. The balance of evidence appears in favour of the assimilation of these proteids by the leucocytes. It is, of course, not clear whether the leucocytes convert peptone wholly or partly into serum albumin, or whether they carry the peptone as such to the cells throughout the body, to be converted by these cells into the blood proteids, serum albumin, and serum globulin. If the serum albumin of the blood were derived merely from the direct transformation of proteid food, one would expect its quantity to diminish in the blood during starvation. As a matter of fact the two proteids, serum albumin and serum globulin, are maintained at about the normal ratio during starvation, and show little diminution from the normal proportions. It thus seems probable that both these substances are formed during cell metabolism throughout the body.

I have mentioned to you that when peptone is injected into the blood it soon disappears from the circulation. This is true also of the albumoses, although if these bodies be introduced in considerable amount they reappear as such in the urine. It is not quite clear whether albumoses are ever taken up from the intestine in sufficient quantities to make them reappear as albumoses in the urine. There are a few observations which indicate that this sometimes happens. It is also well established that albumoses occasionally appear in the urine in conditions apparently unconnected with disturbance of intestinal digestion. Albumosuria has been found most often in suppurative processes, in which pus is retained and disintegrated, in acute infectious diseases, and in some tumours of the bone. How it originates in these cases is not known. The presence of persistent and considerable albumosuria is of considerable prognostic value, since it is almost always associated with an early fatal issue. The cases which we now speak of as albumosuria were formerly described as instances of peptonuria. But it has been almost conclusively shown that peptones do not occur in the urine in pathological states, and that the substances formerly described as such are in reality albumoses.

Even at the present time there is some difference of opinion as to what properties of proteid substances characterise an albumose. The bodies usually described as albumoses are almost invariably mixtures of several different closely allied substances, which vary from one another in their solubilities and in the conditions of precipitation. The different albumoses when in solution are not precipitated by heat alone, and if precipitated by acids or salts are redissolved by boiling, to separate out again on cooling. The albumoses like albumin are precipitated by nitric acid, ferrocyanide of potassium and acetic acid, sodium chloride and acetic acid, and by ammonium sulphate, but unlike albumin are not coagulated by boiling. The chief feature of difference between albumoses and peptones is that the albumoses are insoluble in a saturated solution of ammonium sulphate, whereas the soluble peptone is not precipitated by this reagent. Both albumoses and peptones give the biuret reaction readily in the cold.

I have not yet said anything to you about the nature of the chemical change involved in the conversion of albumins into albumoses and peptones. The truth is that the precise character of the alteration is not understood, but there is reason to think that the albumoses and peptones arise from a cleavage and hydration of the native proteid molecules. This process of proteolytic cleavage reminds one strongly of the hydrolytic cleavage of starch into dextrins and sugars.

In the text-books of physiology you will find many references to a separation of proteid bodies into distinct anti- and hemi-groups during digestive proteolysis. Antipeptone received its name from the reputed fact that this body resisted further cleavage during peptic and tryptic digestion. Hemi-peptone, on the other hand, was split into simpler molecules (leucin, tyrosin, &c.) by the action of the tryptic ferment. Now it has been shown quite conclusively by Kutscher that prolonged tryptic digestion almost completely transforms proteids into amido-bodies, like leucin, tyrosin, aspartic acid, &c. Thus there is no real ground for the separation of anti- and hemi-bodies, and I think we shall do well to lose sight of anti-albumose, antipeptone, hemi-albumose, hemi-peptone, &c.

Perhaps the following scheme will help you to recall the

products of tryptic digestion, and to contrast them with those of peptic digestion in the stomach :—

Peptic digestion.		Tryptic digestion.
Proteid. (Egg albumin, fibrin, &c.)		Proteid. (Egg albumin, fibrin, &c.)
Acid albumin		Alkali albumin
Albumoses		Albumoses
Peptone		Peptone
	Lysin, argenin, histidin, leucin, tyrosin, aspartic acid, ammonia, &c.	

I must not omit to remind you that in normal human digestion the final products of tryptic activity are formed only in small amount, the proteids being absorbed as albumoses and peptones. On the other hand, the final products of tryptic digestion in the laboratory represent the cleavage of all, or nearly all, the peptone.

I have already referred to the caloric value of the proteids. This, you will remember, is almost exactly the same as that of the carbohydrates. You will recall also that the quantity of proteid daily taken by a man of average weight supplies only a small proportion of the total caloric requirement. Thus 100 grams of proteid would yield 410 large calories gross, or less than one-sixth of the caloric needs of a man weighing 70 kilos. But 100 grams of proteid, while falling so far short of the caloric requirements, would ordinarily suffice to replace the nitrogenous cell waste from the body of such an individual, and a considerable increase in proteid would be unnecessary and might, in fact, be embarrassing to normal digestion. You can very easily form some conception of the relationship between the nitrogenous cell waste and the proteid required for its replacement. A man of average weight excretes from 25 to 30 grams of urea daily while in health and performing a moderate amount of physical work. This quantity of urea is equivalent to about 12 to 15 grams of nitrogen. Now it is customary to express the relationship between the nitrogen content of the proteid molecule and the weight of the entire proteid molecule by means of the number 6·25, which is known as the nitrogen factor. That is to say, we can form an approximate idea of the amount of nitrogen in a given amount of proteid material by dividing with the nitrogen

factor, or we can estimate the proteid equivalent of a given quantity of nitrogen by multiplying the weight of nitrogen by this factor. If we multiply 15 grams of nitrogen by 6·25 we get 93·75 grams of proteid material as representing the proteid waste of the body for twenty-four hours. Under conditions of healthy digestion an intake of 100 grams of proteid material or thereabouts would suffice to replace this proteid waste. The shortage in caloric supplied by the proteid constituent of the food must of course be made up by fats and carbohydrates.

I think I have already told you it is not improbable that fat can be formed from proteid, since the proteid molecule contains a carbohydrate moiety and since, as is well known, carbohydrate material can be converted into fat. It is unlikely that fat is actually produced from proteid under normal conditions. The carbohydrate portion of the proteid molecule is probably burned promptly as it splits off from the proteid molecule in the course of metabolism, and this burning is probably so complete that a synthesis of fat cannot ordinarily occur.

I wish now to call your attention to some of the chief forms in which proteid food is employed. It is impossible to give you detailed analyses of the different food-stuffs at our disposal or to describe them in full. For such details you must consult the various works on dietetics. But I hope to be able to indicate to you some of the general principles that should determine your use of the different kinds of proteid food.

One of the first questions to force itself upon our attention is the relative merits of animal and vegetable proteids. There is certainly a close resemblance chemically between the proteids that are furnished by animal and vegetable food. Certain differences in chemical composition distinguish the vegetable proteids from one another and from animal proteids, but as yet we have no satisfactory knowledge of the real significance of these differences to the processes of nutrition. We know, however, that there are great differences in the character of the associated materials of food, and it is likely that one important difference in the nutritive value of the animal and vegetable food is to be sought in the extractive bodies, the salts, the carbohydrates material, &c., with which the two kinds of proteid are usually bound up. In general it seems probable that the vegetable proteids

are more slowly digested than the proteids of animal origin. In many instances this leads to favourable conditions for excessive putrefaction in the intestine. The proteids of meat are supposed to be more rapidly digested, and in some pathological conditions this is a matter of importance. It is likely that in the case of persons in good health the proteid food might be taken almost indefinitely and exclusively either in the vegetable or animal form. But in most gastric and intestinal disorders this is not the case. In gastro-enteric affections of a chronic character it is generally desirable to have both kinds of food represented, since it is rarely advisable to exclude milk and meat from a dietary or to exclude all vegetable food. In fact, even for persons in robust health, it seems undesirable to permit the long-continued use of an exclusive animal or vegetable diet in the climate in which we live.

The most important of all proteid-containing foods is milk. In milk the newly born mammalian animal finds the nutriment best adapted for the rapid growth of the organism. That milk should suffice for the needs of the body during infancy without the addition of other forms of food is due to the fact that this natural food is lacking in none of the representative food-stuffs. Thus cow's milk ordinarily contains from 3 to 4 per cent. of proteid, from $3\frac{1}{2}$ to $4\frac{1}{2}$ per cent. of fat, and about $4\frac{1}{2}$ per cent. of carbohydrate material in the form of milk-sugar, or lactose. The proteid and fat usually vary proportionately. Milk usually contains nearly 1 per cent. in salts. Human milk differs from cow's milk in containing a smaller proportion of proteid and a larger proportion of milk-sugar, differences which render mother's milk distinctly more suitable for the human infant than cow's milk. The proteid of mother's milk is also better suited to human digestion than that from cow's milk. This is partly owing to the larger proportion of albumin and the smaller proportion of casein in human milk. Differences in the chemical constitution of human and cow's casein are doubtless responsible in part for the difference in digestibility.

In order to maintain the caloric needs of the body in a healthy adult from three to four litres of milk are required in the day if milk be used exclusively. You can readily understand that the use of so much fluid is often objectionable by creating discomfort in the digestive apparatus and

through occasioning an excessive flow of urine. In persons not confined to bed it is only rarely advisable to make use of an exclusively milk diet, and such a diet should seldom be continued more than a few days at a time.

There are certain important peculiarities relating to the digestion of milk which it is essential for you to bear in mind. One of these is that of all forms of proteid food milk requires for its digestion the smallest secretion of gastric and pancreatic juice—that is, the weakest digestive juices in proportion to its content of nitrogen. Pawlow's experiments on dogs show that, as compared with the secretion induced by meat, the secretion of gastric juice under the influence of milk is far more economical in that it imposes less work on the digestive glands, and observations on the human subject accord with these results. This is one of the considerations which should always be thought of in estimating the nutritive value of a food-stuff, for if the amount of work done by the digestive glands is too large in proportion to the nutritive value of the food the process of nutrition is being carried on in an uneconomical way. The energy expended by the digestive glands reduces the total energy available for other purposes than digestion.

The economical digestion of milk is thought to be referable in part to the inhibitory action which the presence of milk-fat exerts on the gastric juice, and in part to the inhibitory influence of the alkaline salts of the milk upon the pancreatic juice; but perhaps the chief reason is the difference between the chemical nature of casein and the meat proteids.

In dogs on a milk diet the output of nitrogen as urea has been found to be increased only to 12 or 15 per cent. of the nitrogen ingested during a lapse of from seven to ten hours, whereas in the case of a diet of bread containing an equal amount of nitrogen this increase in nitrogen of urea may amount to nearly 50 per cent. of the nitrogen ingested. This is only another way of saying that the nitrogen of milk is more readily retained in the body than is the nitrogen of other foods. Practical experience clearly shows that milk is, under normal conditions, the best muscle-building food.

Another highly distinctive feature of milk is its influence in reducing the putrefactive processes which go on in the intestine upon an ordinary mixed diet. Under normal conditions, and in many states of impaired digestion, the

reduction of intestinal putrefaction upon a milk diet can easily be demonstrated. The clearest evidence of this effect on putrefactive decomposition in the intestine is derived from the study of the ethereal sulphates in the urine and from the changes observed in the indican. To this subject I shall return in a later lecture. I will only say here that this effect of milk on the putrefactive processes in the intestine is responsible for much of the improvement that occurs in the digestive and general symptoms of many patients who from time to time live on a diet consisting largely of milk. Still another influence of milk upon nutrition is that which it exerts on the excretion, and presumably on the formation, of uric acid. In health a person on a milk diet excretes about one gram of uric acid to fifty grams of urea. On a milk diet the proportion is usually altered to about one to seventy-five or one to eighty. This influence on uric acid excretion is observed also in disease, and depends partly on the fact that the casein yields no nuclein, a point to which I have already referred. But it is also probable that this influence of milk in diminishing the relative and absolute excretion of uric acid is dependent partly on the effect, just mentioned, of restricting intestinal putrefaction.

The foregoing considerations must render it clear to you that milk has an important place in the therapeutics of diet. For one or more of the properties I have just enumerated milk is extensively employed in fevers of all kinds; in acute and chronic gastro-enteric derangements; in diseases of the liver, especially in fatty and cirrhotic livers; in all states attended by an excessive excretion of uric acid; and in many instances of acute and of chronic nephritis.

Over against these numerous and important indications for the use of milk I must now place certain objectionable features which make themselves felt, not indeed generally, but in the case of certain individuals. There are many persons who dislike the taste of milk, and whose prejudice in this respect is so strong that it may be almost impossible to overcome. In such instances it may be well not to attempt the administration of milk as such, but to recommend it in the form of custards or junket. The junket is easily prepared by the use of a small amount of rennet ferment, and if a moderate quantity of some palatable wine, such as sherry, be added before coagulation takes place, it often happens that the milk can be at least tolerated, when

otherwise it would have to be abandoned. The use of junket tablets, such as Hansen's, is convenient for making junket. In some patients the use of milk is followed by nausea, which may be exceedingly annoying. I have found that this can usually be corrected by reducing the quantity of fat in the milk. Instead of giving the patient milk containing 4 per cent. of fat, cut down the fat to 2 per cent., or have the milk skimmed, since in this condition it contains only about 1 per cent. of fat. It is an easy matter in the large cities to get milk of just the right composition, not only as regards fat, but as regards casein, milk, sugar, and salts. This is owing to the establishment of the Walker-Gordon and other milk laboratories, where milk is accurately modified in composition to correspond to the physician's prescription. I strongly advise you to learn the chief indications for modifying milk in composition in order to adapt it to the special needs of your patients. Such modification is frequently essential to a successful treatment of children suffering from digestive disorders, but you will find that a knowledge of these modifications is equally useful to you in the treatment of adult patients. It is not always necessary to have the accurate modifications of milk which are made at the milk laboratories. You can approximate the composition which you desire by means of certain rules which have been carefully formulated by practical students of the problems of milk modification. I cannot do better than to refer you for details to the admirable chapters on this subject in Holt's work on the diseases of infancy and childhood.

In young children and infants an excess of fat in the milk not rarely gives rise to vomiting, or at least to regurgitation of food. You can easily correct this by making a suitable reduction in the fat content of the milk. An excess of fat in other instances appears responsible for the appearance of greenish stools, especially during early infancy.

Another objection to the use of milk is that it often produces excessive peristaltic activity. This is due mainly, I think, to the large volume of fluid, and you will generally find that water gives rise to similar disturbances in the persons who have this experience with milk. Something can be done to avoid exciting excessive peristalsis by cautioning patients to drink milk slowly and in sips, instead of gulping it down as if it were water. It is also helpful to have the milk warmed. It may be, however, that you will

have to advise the use of milk in the coagulated form, that is as junket, from which a considerable portion of the water may be separated as whey. Occasionally, too, I have found that the use of a large quantity of milk renders the urine somewhat irritating from undue acidity. This can be corrected by the simultaneous use of a small amount of milk of magnesia. In some patients the use of milk is followed by a sense of discomfort in the epigastric region, which is apparently connected with the formation of a dense and tough clot. The density of the clot appears to depend in part on the percentage of casein and lime salts and in part on the degree of acidity of the gastric juice. If we dilute the milk with an equal volume of water, its digestibility is increased in consequence of the formation of relatively tender clots. The use of so much water renders the milk unpalatable, but by substituting a carbonated saline water like Vichy we obtain a mixture which is usually well tolerated and agreeable. Or we may render the clot less dense by the addition of lime water in the proportion of one part of lime water to two of milk. It occurs to one that the addition of lime would favour the production of a denser clot than ordinarily is formed, but this is not the case. The lime given probably renders the lime salts of the milk less soluble, and so modifies their usual influence in the production of clotting.

Many persons complain that the use of a considerable amount of milk is followed by constipation. This is probably owing entirely to the large extent to which the ingredients of milk are absorbed. The inclination to small and infrequent movements can be usually corrected by increasing the quantity of fat in milk. There are times, however, when this is impracticable, and it may then be necessary to allow the patient to take a larger amount of vegetable food, such as spinach or celery, in order to derive fæcal bulk from the cellulose. There are cases of acute gastritis and of acute gastro-enteritis occurring both in children and in adults where the digestive disorder has arisen on a diet in which milk has formed a large part. The disturbance either may be due to the contamination of the milk with micro-organisms outside the body, or may arise from the activity of bacteria already in the intestine, and not introduced with the milk. Whatever may be the origin of these acute disturbances, the practical point for you to remember is that milk should be

completely withdrawn for the time being from the dietary, and that many days must elapse before milk can be used even in small amounts. I have known the incautious return to the use of milk to be the occasion of fatal exacerbations of gastro-enteric disease.

There are two peculiarities of the composition of milk which render it undesirable to continue its exclusive use for very long periods of time. One of these is the fact that milk has a low content of chlorides, on the presence of which, as I shall show you later, many of the important physical processes, including osmosis, are closely dependent. The other peculiarity is the low content in iron which favours the development of anæmia when milk is the exclusive article of diet. During the first year of infancy the low content of iron is no objection to an exclusive milk diet, as the tissues at birth contain sufficient iron.

Milk is employed in a number of different forms as an article of food, and I desire to say a word in regard to some of these. The use of peptonised milk has been extensive in recent years, and has proved exceedingly useful as a temporary expedient in many forms of digestive disturbance. The process consists in the partial conversion of the casein into albumoses under the influence of a proteolytic ferment. Such a ferment is present in the extractum pancreatis prepared for use in what is known as the Fairchild process, one of the most satisfactory methods of peptonising milk. According to this method one can either partially or completely peptonise milk. The partial peptonisation usually suffices, and has the great advantage over the complete process of giving only a slightly bitter taste to the milk, since the quantity of albumoses and peptone is small. The peptonising powder can be obtained in small tubes containing five grains of the pancreatic extract which holds the tryptic ferment and fifteen grains of sodium bicarbonate. These substances are added to one pint of milk which has been diluted with four ounces of water. The mixture is then kept at a temperature somewhere between 105° and 115° Fahr. for ten or twenty minutes. The peptonising process can at any time be arrested by boiling the milk or cooling it on ice, the latter plan being preferable.

You will find peptonised milk exceedingly useful in patients, both small and large, in whom there is an acute gastritis or gastro-enteritis, in whom you cannot expect the

stomach and intestinal juices to carry on the normal proteolytic activity. Do not, however, get your patients in the habit of taking milk in the peptonised state for a long period of time. Such a habit is certainly detrimental, probably because it removes to a considerable extent the normal stimuli to the secretion of the gastric and intestinal proteolytic ferments. In other words, you run the danger of allowing certain secretory cells to get into lazy habits from which it may be difficult subsequently to arouse them.

In this connection it is convenient to refer to the sterilisation of milk. This can be accomplished by boiling milk for twenty minutes or by exposing it for forty minutes to the action of a temperature of 167° Fahr. In both cases one destroys all pathogenic micro-organisms, but in the second process, which is known as Pasteurisation, spores are not destroyed. It is essential for you to bear in mind that the destruction of these micro-organisms does not necessarily affect such bacterial products as may be present in the milk at the time of exposure to the sterilising temperature. In other words, if the milk has already been spoiled through the production of bacterial poisons these poisons may act as detrimentally as if the milk had not been sterilised. Milk sterilisation thus protects against bacteria, but not necessarily against their products.

When the practice of sterilising milk by boiling first came into use it was thought to be an ideal method of destroying germs. It was soon discovered that there are decided drawbacks to the process, especially in the case of children. The casein is rendered less digestible through boiling owing to some chemical change which is not fully understood, and the milk sugar is to some extent converted into caramel. Moreover the prolonged use of sterilised milk appears in some instances to have led to the development of scurvy. These are serious objections to sterilisation by boiling. The Pasteurisation already referred to is distinctly preferable. It is possible that even the temperature 167° Fahr. induces changes in the casein, but as far as we know at present they are practically unobjectionable. Exposure for ten minutes to this temperature suffices to kill most pathogenic organisms, and yet does not impart a boiled taste to milk. If the Pasteurised milk be rapidly cooled below 50° Fahr. it will remain sweet for about thirty-six hours longer at ordinary temperature than milk not Pasteurised, but from which

germs have been excluded by ordinary precautions. Where one wishes to preserve milk for long journeys it is necessary to kill the spores, and for this purpose boiling is essential.

The efforts which have been made to preserve milk by the addition of salicylates, borates, formalin, or other antiseptics have not met with favour. Nevertheless I think the use of milk so preserved much less objectionable than milk very rich in micro-organisms. Dr. Park tells me that one part of formic aldehyde (formalin) to 50,000 parts of milk prevents the multiplication of bacteria. Now there is no reason to think that formic aldehyde, which is readily oxidised by the organism to formic acid, can act as a gastro-intestinal irritant in this dilution. After absorption in such amounts as would be taken in it can do no harm, since the formic acid into which it is oxidised is as readily burned by the cells as alcohol. It seems to me that milk preserved by formalin could advantageously be used in summer, especially by the poor.

It is important for you to know that bacteria sometimes induce chemical changes in milk which lead to severe symptoms of poisoning, such as repeated vomiting, diarrhœa, headache, great prostration, and fever. The victims of such poisoning, which may be epidemic, usually correspond to one particular milk supply. We know nothing of the chemical nature of the bacterial poisons concerned with such disturbances as those to which I refer, but some persons appear to derive satisfaction from referring to them by the euphonious name of 'galacto-toxins.' Milk which contains bacterial poisons capable of creating serious digestive disorders may be coagulated, and may not taste like good milk, but generally it is impossible to judge of its toxic nature from its appearance or taste. On the other hand, milk may be coagulated by the commonly present lactic acid organisms without being injurious.

You will often be asked by your patients with digestive derangements whether it is proper for them to eat cheese. The answer to this question depends in a considerable degree upon the kind of cheese that is wanted. Many patients with chronic disorders of gastric and enteric origin can take a small amount of freshly made pot-cheese without any deleterious results. As a rule the use of old cheese is inadvisable in chronic dyspepsias. There is, however, some choice as to such cheeses. A recent investigation of the

subject by Dr. Vaughan, of Michigan University, shows that most forms of cheese contain an indol-producing bacillus of the colon class. This organism was toxic to small animals. Only four cheeses out of a considerable number did not contain this organism. They were Roquefort, genuine Swiss, and genuine French cheese and sap sago. It is not clear whether this organism is distinctly deleterious when cheese is eaten by healthy people, but it is certainly best not to advise the use of cheeses which contain indol-producing organisms for persons who are dyspeptic. Most cheeses also contain a peptonising germ which improves the digestibility of the casein. In all acute and subacute gastro-enteric states it is best wholly to avoid the use of cheese.

I have already mentioned to you some of the uses of skimmed milk. You will find comparatively few adults who are unable to take a fair amount of milk from which the fat has been largely removed. Buttermilk is frequently useful as a preparation from which the fat has been very largely removed. It has the advantage that the churning process and the moderate lactic fermentation have caused the formation of small flocculi of casein which are readily digested. The lactic acid present is unobjectionable, but some persons greatly dislike its taste. Matzoon and kumyss, or, more properly, kephyr, are favourite forms of fermented milk. Kumyss is fermented mare's milk. Kephyr is a modern substitute for kumyss, prepared by fermenting cow's milk with kephyr grains. These resemble little bits of cauliflower, and owe their fermentative action mainly to the saccharomyces mycoderma, though they contain also lactic acid-forming organisms. The fermentation is thus a double one. The lactic acid organisms change a part of the sugar into lactic acid. The vinous ferment decomposes a part of the sugar into alcohol and carbon dioxide, while destroying a very small part of the proteid of the milk. The fermentative process is permitted to go on to a point where there is a production of from 0·6 per cent. to 2 per cent. of alcohol.

In making kephyr from cow's milk it is necessary to approximate the composition of mare's milk by diluting the cow's milk and adding a certain proportion of sugar.

It is important to bear in mind the changes undergone by the sugar and the casein in the preparation of kumyss or kephyr. The sugar is very largely replaced by lactic acid,

alcohol, and carbon dioxide. The casein is precipitated in the presence of lactic acid, as in the ordinary process of souring, in the form of flocculi, which are broken up into a state of fine division by the agitation to which the fermenting fluid is subjected. The casein is thus in a state which fits it for rapid digestion and absorption. The carbon dioxide and alcohol stimulate the secretion of the gastric juice, which is only slightly excited by the presence of ordinary milk. In the case of some patients it is desirable to let a portion of the carbon dioxide escape before the kumyss is drunk.

Matzoon is prepared by a process somewhat similar to that employed in making kumyss. The ferment which is added consists of some form of yeast and of several different lactic acid-producing bacilli. The milk is first boiled to insure sterilisation, and, after addition of the micro-organic ferments, the fermentation is carried on at about 105° Fahr., a part of the time in an open vessel. The fermentative process is checked by reducing the temperature. A slow fermentation continues after bottling, and the older matzoon contains more lactic acid and somewhat more alcohol and carbon dioxide than that which is freshly made. The quantity of alcohol and of carbonic acid is very much less than in kumyss. The consistence of matzoon is thick and cream-like.

Both kumyss and matzoon are useful as foods in the treatment of acute and chronic digestive disorders. They are often retained and digested where ordinary milk is vomited. One great advantage of both these preparations is the fact that the casein has been precipitated and broken up into small masses, so that large coagula are not formed in the stomach. The indications for the use of these forms of fermented milk are much the same, but matzoon is often preferable to kumyss owing to its comparative freedom from carbon dioxide. The thick consistence of matzoon renders it desirable in many instances to dilute it somewhat. Matzoon is considerably richer in fat than is kumyss, and this may be a feature of some importance where the use of fat is desired or has to be shunned. There are many instances where you will have to leave to your patient the choice between these two varieties of fermented milk, since individual taste and tolerance differ so much in regard to them.

Condensed milk, made by heating fresh cow's milk to the

boiling-point for the purpose of destroying bacteria and then evaporating in vacuo at a low temperature, is a preparation much employed, especially among the poor, in the feeding of infants. The preservation of condensed milk is accomplished by adding about six ounces of cane sugar to the pint. Fresh condensed milk, however, can be obtained to which no sugar has been added. As a rule the milk is considerably diluted for use. While exceedingly useful as a temporary food condensed milk is highly objectionable for the prolonged feeding of children. The objections are that it contains too little casein and too little fat, food constituents essential to the normal development of infants. As a matter of fact you will see among dispensary children fed on condensed milk a considerable proportion who have signs of rickets. The advantages of condensed milk as a temporary food are that it has been sterilised, that the casein in the considerable dilution in which the milk is employed is present in such small quantities that even infants with feeble digestion can take it, and that it contains an abundance of sugar, which is the easiest food for an infant to digest and absorb. Children fed largely on condensed milk often grow large and flabby from the use of so much sugar.

A German preparation of casein known as caseon or plasmon has recently been introduced in this country. It is prepared by precipitation of the casein from fresh milk. The casein is then dissolved in sodium bicarbonate in the presence of free carbon dioxide, which prevents the decomposition of the casein by the alkali. The casein thus prepared is dried to a yellowish-white powder almost without taste and without odour. It is partly soluble in water, and in part imbibes water and swells. Caseon contains nearly 2 per cent. of fat and about $2\frac{1}{2}$ per cent. of milk-sugar. A valuable feature is the large content of salts, which amounts nearly to 7 per cent. Caseon has been found useful as a substitute for milk where a considerable quantity of fluid is undesirable. The statement is made that caseon neutralises more than three times as much acid as an equal weight of beef, and hence is especially useful in treating hyperchlorhydria. It has not yet been extensively tried in this country, but promises to be a convenient form of proteid food.

Whey, which is prepared by coagulating milk by means of rennet and straining off the fluid which separates, is particularly useful for young infants with acute digestive

derangements. It contains a considerable percentage of milk-sugar, but is low in salts, and of course very low in proteids and fat. It is often retained in the stomach when almost everything else is rejected. It should be given frequently in small amount. Whey is rendered more palatable by the addition of a little brandy or sherry. It is best to give it cold.

It may seem to you that I have devoted a disproportionate amount of time to the discussion of the preparations of milk, but I do not think this is really the case. Milk forms so important a part of the dietary of invalids that you should be familiar at least with the more important ways in which the different constituents of milk can be utilised in practice.

There are two other forms in which proteid food is very much used, and about which I must say a word. These foods are eggs and the muscles of mammals and birds. The two parts of fowl's egg, the yolk and the white, are very different in their chemical nature. The white consists almost wholly of 'egg albumin,' which is not a single substance, but a mixture of proteids. This proteid material is easily and rapidly digested in the raw or slightly cooked condition, but when firmly coagulated may be only slowly acted on by the digestive juices. The egg-yolk contains, in addition to a small amount of albumen, a large quantity of fat, much lecethin, probably an ethereal compound of cholin with glycero-phosphoric acid combined as glyceride with stearic and palmitic acids, and certain colouring matters. Owing to the presence of the fat and lecithin the yolk is more apt to cause digestive derangements than the white. I shall have occasion later to show you that lecithin under some circumstances breaks up in the intestine into two basic nitrogen-containing bodies known as neurin and cholin. When present in considerable amount these bodies seem capable of giving rise to serious toxic symptoms.

I have found it inadvisable to make use of the yolks of eggs, except with some caution, in persons strongly inclined to constipation. The whites of the egg can, however, be safely employed under these circumstances. Many people will tell you that they are made 'bilious' by eating eggs. They usually mean by this that the use of eggs is followed by headache and some degree of lethargy. I am inclined to think that these symptoms, which undoubtedly arise in

certain persons, are connected with the imperfect digestion and excessive putrefaction of proteids belonging to the egg-yolk. These symptoms are especially apt to come on where there is an inclination to constipation. In some persons one egg suffices to bring them on, in others they appear only when two or more have been eaten. In a child of four years a single egg-yolk regularly sufficed to bring on a sharp rise in temperature. Here there was an habitual condition of excessive intestinal putrefaction. I do not know how to explain this idiosyncrasy.

I have found it useful in persons who have difficulty in digesting eggs to prescribe the whites of three eggs with the yolk of one. By doing this you can often avail yourself of the valuable nutritive properties of eggs without the risk of disturbing digestion. The free use of eggs is often helpful in the treatment of carbohydrate fermentation, as there is nothing in the egg that affords suitable material for such fermentation. The caloric value of an egg is fairly high in proportion to its bulk. It is about seventy large calories. Two eggs yield about as much caloric energy as one tumbler of ordinary milk.

The proteids of meat are present as albumin, myoglobulin, myosin, &c. Besides its proteid elements meat contains a fair quantity of fats and salts, especially phosphates. Extractive materials, that is to say nitrogenous substances soluble in alcohol, are present in considerable amount. The extractives in meat like beef, lamb, &c., amount to about 0·2 per cent. The presence of these extractives acts as an agreeable stimulus to the appetite. They are hence much used in the preparation of soups. The influence of the extractives upon nutrition has been considerably discussed, but we have very little definite knowledge on the subject. It is customary among physicians greatly to restrict the use of meats in cases of nephritis. This limitation is sometimes carried so far as to exclude red meats altogether from the dietary of the patient. The reason given for this exclusion is that the extractives act injuriously on the kidney. I am inclined to think that this effect has been greatly exaggerated, and am disposed to allow my patients with nephritis to eat a certain amount of red meat, especially where there is an inclination to lose strength when meat is excluded. I think it much better to throw a slight additional burden on the kidneys than to run

a serious risk of weakening the general powers of a patient with chronic kidney disease. It seems to me likely that the greatest advantage which milk has over meat as a proteid food, both in digestive derangements and in renal disease, is its slighter yield of putrefactive products. I consider this more important than the difference in the quantity of extractives. It may interest you to know that I have in my laboratory a dog of medium size which for more than six months has taken, in addition to meat, from 20 to 40 grams of Liebig's extract of beef daily. The animal appears in the best of spirits, and is very active when released from the cage. He has not a trace of albumin in the urine, although he has been excreting very large quantities of extractives for so long a period.

Another reason why milk is to be given the preference to meat in cases of chronic disease of the kidney and of the liver is the relatively slight yield of ammonia that accompanies the absorption of the albumoses and peptones derived from casein. I told you a short time ago that ammonia is formed in small amounts in the human intestine as an end-product of the tryptic digestion of proteids. I also mentioned that in addition to the ammonia arising in this way within the lumen of the intestine a considerable amount of ammonia is split off from the proteid molecule during digestion in the wall of the intestine, very likely by the action of lymphoid cells upon proteids passing through the wall of the gut. Now it has been shown by the experiments of Selaskin that the quantity of ammonia arising in this way is much greater in the case of a meat diet than in the case of a milk diet. The clinical importance of this fact will occur to you on considering what becomes of the ammonia arising in the manner just described. The ammonia split off in the intestinal wall passes by way of the mesenteric and portal veins to the liver. In the liver this ammonia undergoes the same fate as the ammonia which comes from the cells generally, that is, it becomes converted into urea. On a meat diet the blood of the portal vein contains a high percentage of ammonia, and hence yields considerable urea in the course of twenty-four hours. This urea, which apparently does not represent the nitrogenous waste of cells, must therefore be regarded as imposing an unnecessary tax on the kidney as well as on the liver. On a milk diet, owing to reasons but little understood, but doubtless con-

nected with the chemical constitution of casein, this alimentary urea is small in amount, and has no influence in overburdening the cells which perform the synthesis of urea and take part in its excretion.

It is a matter of practical observation that people often grow nervous and irritable on a dietary containing too liberal an allowance of meat. These persons may be greatly benefited by considerably reducing this allowance. It is customary to allow patients to eat the meat of chicken and other white meats in cases where red meat is interdicted on account of its extractives. This is a little surprising in view of the fact that white meat of chicken actually contains as much or more extractive material than beef. There is often something to be said, however, in favour of white meats on the score of their greater digestibility, perhaps owing chiefly to a smaller quantity of connective tissue. Let me remind you of the relatively large nuclein content of the meats of young animals. Owing to the effect on uric acid excretion it is undesirable to use meats of this class, such as veal, where patients are excreting an excess of uric acid. For the same reason the various sweetbreads must be excluded, especially the 'heart bread,' or thymus.

The various beef extracts now on the market resemble one another in being made up largely of extractive materials. They differ a good deal, however, in the amount of soluble albumins which they contain. They also differ a good deal in respect to salts. For details as to these matters I refer you to books on dietetics. The point which I wish to make here is that all these beef extracts have a certain utility which they owe to the stimulation and refreshing effects of the extractives. Some of them, however, have no other virtue than this and are not to be regarded as foods, since they pass through the body without yielding energy to it through their metabolic decomposition. One of the best preparations is that known as Mosquera's beef meal. It is not only palatable, but contains a considerable amount of soluble proteids which give it a value as a food.

The preparation called somatose has recently come into prominence as a food. Somatose is a mixture of albumoses obtained from the action of a ferment on meat proteids. It is therefore a predigested food. There are conditions in which somatose is useful on account of the readiness with which it is absorbed. The indications for its use are much

the same as for peptonised milk, but it has the advantage over peptonised milk of not necessitating the use of much fluid. While this concentration is certainly advantageous at times, it also has its drawbacks, the chief one being that it is very liable to set up excessive peristalsis and more or less pain. When cautiously employed in conjunction with other food-stuffs it is sometimes distinctly helpful for short periods of time on account of its ready absorption.

The last kind of food to which I shall refer to-day is gelatin, a substance of peculiar interest to the physiologist, for the reason that while closely resembling the proteids in many chemical characters it differs from them in the highly important respect that it is incapable of replacing proteid waste by building up cell material. The resemblance to proteids relates to elementary composition, to the conversion into peptones by digestion, to metabolic decomposition and oxidation into urea, carbon dioxide, and water, and to the yield of leucin (α-amido-iso-butyl-acetic acid) and glycocoll (amido-acetic acid) under suitable conditions. Gelatin gives the biuret reaction, but as it contains no tyrosin radical it does not react with Millon's reagent.

Notwithstanding gelatin contains nitrogen it must be regarded as a non-proteid food, because it cannot replace the proteids of the diet except to a limited extent. Like the carbohydrates and fats, it saves proteid waste, and it is possible to remove from the diet a certain amount of proteid if this be replaced by gelatin to an amount equal to about twice the caloric value of the gelatin. According to one estimate one-fifth of the ordinary quantity of proteid may be so replaced; according to another the quantity is considerably larger than this. It seems clear that gelatin is really more efficient as a saver of proteid than either carbohydrates or fats, and I am inclined to believe that we might make more extended use of gelatin as an element of the dietary of patients who show proteid waste. A practical advantage of gelatine is its ready digestibility and absorption, but it must be remembered that patients soon tire of its use in considerable amounts.

Gelatin is obtained by boiling collagen with water. The process involves the appropriation of water, is in fact an hydration process. The collagen which yields gelatin is an important constituent of connective tissues and the ossein of

bones. One might perhaps suppose that this collagen can be replaced by gelatin, but there is some experimental evidence that this is not the case, and that collagen is made only from proteid food. Gelatin introduced into the circulation is not assimilated, but reappears in the urine. It has, however, the property of increasing somewhat the coagulability of the blood, and efforts have been made to utilise this fact in the treatment of aneurysms where it is the desire to favour local clotting—with what success I am unable to say. It is also stated that the hæmaturia of hæmophilia has been checked by free use of gelatin as a food.

I have mentioned that the decomposition of gelatin yields no tyrosin. Might we not make use of this peculiarity of gelatin where we wish to limit putrefactive cleavages in the intestine with the production of aromatic substances? It is from the tyrosin of the proteid molecule that we get phenol, and probably indol and other products of the aromatic class. These are the bodies which give us the ethereal sulphates of the urine, and it is conceivable that these substances might be considerably reduced if a portion of the proteid of the food, say one-fifth or one-quarter, could be replaced by means of gelatin. This is, however, only a suggestion for the practical workings of which I would not vouch.

I regret that the time at our disposal does not permit me to discuss with you the chemical properties of many other individual articles of food about which you should know something before entering on the practice of medicine. I strongly advise you to inform yourselves as fully as possible in regard to the chemical and physiological characters of the ordinary articles of food. Many physicians are inexcusably ignorant on this subject, and their patients frequently suffer in consequence.

Another subject on which you should inform yourselves, not only from books, but practically, is cooking. It has often seemed to me that some of the time usually devoted in our medical schools to the study of obscure and obsolete drugs might more advantageously be given to acquiring a practical familiarity with the ordinary processes of cooking. It is certainly true that you will often fall short of your duty as practitioners of medicine if you fail to take account of the manner in which the food of your patients is prepared for use. In very many conditions of disease it makes an

enormous difference to the patient whether he is eating properly raised bread or half-baked dough, whether his cereal foods are coarse and uninviting or thoroughly boiled and soft, whether a large part of his food is badly fried or prepared according to more wholesome methods. If you leave uncorrected the gross errors of cooking which are so often committed, especially in country districts, you will surely fail in your treatment of the diseases of nutrition, no matter how learned you may be in pathological anatomy and chemical pathology.

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LECTURE IV

THE CHIEF FOOD-STUFFS AND THEIR FATE IN THE ORGANISM IN HEALTH AND IN DISEASE.—WATER AND THE INORGANIC SALTS

Conditions in which the water in the organism is reduced—Symptoms of excessive withdrawal of water—Therapeutic indications—Excessive accumulation of water—Salts of the food—Modern advances in physical chemistry—Ostwald's experiment illustrating the wandering of atoms in solutions—Electrolytic dissociation—Toxic action of certain salts in relation to dissociation—Normal solutions—Electrolytic dissociation increases with dilution—The food-salts: their absorption—Sodium chloride: its absorption from the stomach and intestine—Potassium chloride—Carbonates, sulphates, and phosphates—Absorption of calcium salts—Salts of the plasma in health and disease—Constancy in molecular concentration—Dissociation of salts and electrical conductivity of animal body—Effects of reduced ingestion of sodium chloride—Retention of chlorine in fevers and in anæmias—Excretion of phosphates in fevers—Exudates and transudates—Relation of sodium chloride to secretion of free hydrochloric acid—Sodium chloride and renal secretion—Diuretic action of salt enemas—Potassium salts—Calcium salts—Magnesium salts—The phosphates—Acidity of the urine—Phosphaturia—The sulphates—Recapitulation—Mineral waters.

THE large quantity of water (two or three litres) which is daily appropriated by an adult in food and drink, and the equally large or even larger loss of water through expiration, and urine, and cutaneous transpiration, very clearly suggest how prominent is the part that water plays in the maintenance of life processes in man. The water introduced with the food is essential to its solution and absorption. In the blood and lymph and cells it is the necessary vehicle for carrying on the nutritive and excretory interchanges between these cells and fluids. Ultimately it serves the body in the vital functions of carrying off its waste solids by the kidneys and skin, and its waste carbon dioxide through the lungs. In health there seems to be a rough correspondence

between the proportion of water in the tissues and the activity of metabolism. The average content of water in the adult tissues is not far from 64 per cent., but is higher during infancy, and is likewise considerably higher in those individual organs whose cells live most energetically, as the cells of the muscles, liver, kidneys, and nervous system. In the bones, in dentine, and in some other inactive structures the proportion is much lower. Under normal conditions the proportion of water does not vary greatly in the different organs of the same individual, but in pathological conditions the proper water content of the cells and fluids is liable to undergo considerable change. This alteration in the proportion of water in the cells and fluids is sometimes associated with an increased or diminished rapidity in the transit of the water molecules through the body. As physicians you should know something of the ways in which the cells and fluids are robbed of their water or receive an excess, for the consequences of these variations are of practical importance.

It is, of course, evident to you that anything which distinctly reduces the absorption of fluid from the gut must ultimately diminish the water content of the cells and fluids of the body unless there should be at the same time an obstacle to the normal exit of water, which is very unusual. This diminished absorption may come about in several ways. The income of water may be greatly reduced when, for any cause, the quantity of food is diminished. We often see this in fever, and in conditions where the appetite is impaired from any cause. Then, again, the absorption of water is greatly impaired whenever the stomach is unable to empty its contents freely into the gut; for, as you have been already taught, there is little or no water taken up from the stomach. We see this condition in gastric stenoses of various grades, generally in association with dilatation. Often these subjects of gastric disease ingest sufficient water but vomit a large portion of it. An extremely important cause of impaired absorption is acute enteric disease with diarrhœa. The loss of water from diarrhœa is often rapid and great. In proportion to the body weight the loss is frequently very large in the case of infants with summer diarrhœa. In cholera it is also large. Whenever you are in charge of a patient with diarrhœa you should keep a close watch on the water loss, even if the movements are not very

frequent, for you cannot say how soon the deprivation will become an evil prognostic factor.

These are the common ways in which the body is robbed of its water. In diabetes there is an increased loss of water, necessitated doubtless by the demand for water to dissolve the glucose which must be removed. The evaporation from the skin may be so rapid under some circumstances as to remove considerable fluid from the body in a short time. Then, again, the loss of water in acute hæmorrhage may be large enough to be of clinical importance. In all these cases there is normally a strong desire to drink water, and the gratification of this thirst helps to re-establish the normal percentage of water in the organism.

Although physicians have long recognised the harmful effects of a large withdrawal of fluid from the body, our exact knowledge of the effects of this withdrawal is of recent date. Allow me to enumerate for you some of these effects.

A subject in whom the water supply is largely reduced soon feels indisposed for effort, and develops an increasing dislike for solid food. A decided loss in bodily weight goes hand in hand with the growing prostration. The arterial tension falls, as one might confidently predict. Although the specific gravity of the blood serum is somewhat increased, there is little change in the number of red blood cells or in the hæmoglobin content of the blood. In experimental thirst in human subjects there has been found an absolute and relative increase in nitrogen excretion in comparison with the preceding period, and it can hardly be doubted that the metabolic decomposition of cell proteid is stimulated. It is thought that there is some retention of nitrogenous products of decomposition during the thirst period, and that these are not eliminated until water is again freely used. There is, however, no evidence that any of these substances act destructively on the blood. This does not mean that they may not unfavourably influence the cell activities of the body. It has, indeed, been suspected that the slight rise in temperature observed during thirst is referable to such substances.

During a period of thirst the volume of the urine falls greatly, and the amount of insensible perspiration is likewise much reduced. Still the quantity of water that is lost by the lungs, by the kidneys, and by the skin is so much in excess of that which the organism derives by absorption that the

cells of the body are called upon to give up some of their water in order to maintain a fair volume of blood. A further source of water for the blood and lymph is the combustion of fat and proteid and sugar through oxidation. Where the combustion of fat is rapid considerable water may be formed in the body. A reduction in the normal proportion of the water in the central nervous system is perhaps responsible for the mental apathy and stupor observed in some cases of acute disease with loss of water. It has even been suspected that the condition of spasm known as tetany, and not rarely noted where the stomach is greatly dilated, has the same origin. From what I have already said it should be plain to you that considerable losses of water in disease cannot be viewed with complacency. It is clearly your duty as practitioners to take appropriate steps to replace these losses if you cannot prevent them. Fortunately it is by no means difficult to do this in acute disease. The thirsting cells take up water with avidity if they have the opportunity. You can give them this opportunity by introducing an abundance of a physiological salt solution by way of the stomach or rectum; or, if need be, by direct intravenous infusion or by subcutaneous injection into the cellular structure of the abdomen. The replacement of the lost fluid is often followed very promptly by an improvement in the mental state of the patient and by an improvement in strength. This improvement is particularly striking in the case of children exhausted by prolonged diarrhœa. Of course I do not intend to give you the impression that the replacement of water is the only therapeutic indication in such instances; I wish merely to call your attention to the clinical importance of this step. It is probably fair to say that persons sometimes die from a severe water loss, not because the loss cannot be compensated, but because the importance of this drain of fluid is not recognised by the physician.

An excessive accumulation of water in the organism occurs under conditions where the absorption of water is not far from normal, but when for some reason excretion is impaired. The chief causes of such impaired excretion are cardiac weakness, alteration in the walls of the smaller blood vessels, and impaired activity of the renal epithelium resulting from disease. These causes may be in some degree separately operative; very often they are combined.

The accumulation of fluid occurs in the lymph spaces of the cellular tissues and constitutes œdema. A transudation of fluid also occurs under some circumstances into the great serous lymph cavities. Then we have ascites or hydrothorax. Inflammatory conditions, inducing exudation of serous fluid from the vessels of the peritoneum, give rise to similar accumulations. The retention of water in these positions is chiefly important through its mechanical effects. It occasions no general metabolic effects comparable to the effects that follow loss of water on the part of the cells generally.

We occasionally meet with cases of general œdema in which the cells of the various organs after death contain a distinctly higher percentage of fluid than is physiological; but we do not know of any important nutritive derangements that can be attributed to the accumulation of water in this form of œdema.

I wish now to call your attention to the inorganic salts of the food and their fate in the body, both in health and disease. We are apt, I think, to underrate the importance of the mineral constituents of the food. Perhaps this is owing to the fact that the mineral salts, unlike the carbohydrates, fats, and proteids, do not constitute a source of energy to the organism. But while it is true that these substances yield no kinetic energy by their decomposition it is equally true that their presence in certain proportions is essential to the progress of the most important cellular activities. This is owing to their physical properties in facilitating diffusion and in aiding solution. Moreover the inorganic salts must not be regarded as substances quite apart from the organic materials of the body, for the elements which compose these salts enter into the closest relations with the protoplasm of the cells.

The inorganic salts introduced with the food are chiefly combinations of sodium, potassium, calcium, magnesium with carbonic acid (H_2CO_3), hydrochloric acid (HCl), sulphuric acid (H_2SO_4), and phosphoric acid (H_3PO_4). These salts are for the most part soluble in the water taken with the food and in the digestive juices. These soluble salts are ultimately absorbed from the digestive tract and then belong to the cells and fluids of the body. Some of them, like salts of calcium, enter into the formation of the skeleton, and are only slowly liberated for elimination

from the body. Others, like the chlorides of sodium and potassium, pass through the body rapidly and are continuously excreted in considerable quantities, this large excretion being made possible by the considerable quantities of the salts which are regularly ingested with the food.

Some of the salts taken with the food are only in part absorbed from the digestive tract, owing to their slight solubility. This is true, for instance, of the calcium and magnesium phosphates. These bodies are largely discharged with the fæces, and are thus lost to the organism.

The mineral salts which find their way into the body have certain physical and chemical properties, when in solution, which help to explain some of the phenomena of normal and pathological physiology. Only within recent years have we learned, through the admirable studies of Van't Hoff, Arrhenius, Ostwald, and others, how essential are certain conceptions of physical chemistry for the comprehension of life processes. I shall take the liberty of assuming that you are not as familiar as you should be with these conceptions, and shall sketch for you very briefly indeed certain physico-chemical facts without which you cannot hope to obtain a correct idea of the *rôle* of the mineral salts, either in health or in disease. I shall ask your somewhat close attention to this subject, as it is not easy to follow even a simple staement of the facts to which I must refer.

You know that in the case of a solid salt, like dry sodium chloride, the molecules undergo little or no change, and the condition of the salt remains the same indefinitely. If now we dissolve the salt in water, the molecules have an opportunity to take on the more active motion which is thought to be characteristic of substances in solution. If we pass a galvanic current through a solution of sodium chloride, there is a wandering of the chlorine and sodium atoms to the poles. Thus the chlorine atoms move to the positive pole and the sodium atoms pass to the negative pole. This wandering of the atoms is beautifully shown by an experiment which Ostwald devised. A galvanic current was passed through a solution of sodium chloride contained in jars connected by a glass tube containing the same solution. On removing the tube connecting the two jars, and on discharging the electricity held by the atoms in solution, it was found that the number of chlorine atoms was increased in the jar corresponding to the positive pole, and the number of sodium atoms was

increased in the jar corresponding to the negative pole. This increase in the sodium atoms is indicated by the liberation of hydrogen. The liberation of hydrogen is due to the presence of metallic sodium.

On account of their electrical properties the atoms in the salt solution are called anions and cations, or positive and negative ions. Now, according to a well-known physical law, bodies charged with the same kind of electricity repel one another, while bodies charged with opposite kinds attract one another. Hence the cation must be loaded positively and the anion negatively, *e.g.* sodium is a positive ion, chlorine a negative ion.

Carefully devised physical experiments show that whenever salts pass into solution a certain proportion of the molecules undergo separation into their ions. These ions become electrically charged positively and negatively in the moment of their separation. In this important respect they differ from the molecules which do not undergo separation into ions, and in which the positive and the negative electricity neutralise each other. The positively and the negatively electrically charged ions possess a much greater freedom of action than the atoms of the unseparated molecules. This freedom of the ions is known as electrolytic dissociation, and all chemical reactions are based upon it. Thus, if we bring together a solution of hydrochloric acid (HCl) and one of potassium carbonate (K_2CO_3), the following interchange takes place :—

$$\begin{matrix} H \\ H \end{matrix} \!\!\diagup\!\!\diagdown\!\! Cl + \begin{matrix} K \\ K \end{matrix} \!\!\diagup\!\!\diagdown\!\! CO_3 = \begin{matrix} K \\ K \end{matrix} \!\!\diagup\!\!\diagdown\!\! Cl + \begin{matrix} H \\ H \end{matrix} \!\!\diagup\!\!\diagdown\!\! CO_3$$

Here it is the ions that enter into reaction, not the molecules of the salts themselves. You notice that the group CO_3 does not undergo further dissociation, but constitutes the negative ion in the solutions. There are many other instances in which groups of atoms act as ions.

It is important for you to understand that what is known as the poisonous action of many substances appears to be due, not to the action of the molecule as a whole, but of one of the ions. For example, cyanide of potassium is a highly poisonous substance, the action of which is not dependent on the molecule KCN acting as such, but on the CN ion, which is formed when the salt undergoes dissociation in solution. Similarly the corrosive action of sodium or potassium

hydroxide does not depend on the sodium or potassium, but on the hydroxyl ion HO. We may infer this from the fact that the sodium and potassium ions show no corrosive action when they are obtained by dissolving potassium chloride or sodium chloride. In cases where the molecule is not dissociated, but contains the hydroxyl group OH, we fail to find the corrosive action observed in the metallic hydroxides which I have just mentioned. For instance, ethyl alcohol (C_2H_5OH) contains the hydroxyl group; but, as alcohol does not undergo dissociation in water, we fail to get a specific corrosive action of this group of atoms.

The degree of dissociation depends on numerous conditions, as the nature of the material, the temperature, and the concentration of the solution. Of these conditions the most important in relation to physiology and pathology is the degree of concentration.

It has long been customary to express the concentration of a solution by the absolute weight of the substance dissolved. Thus a solution of one gram of sodium chloride in 100 grams of water is a one per cent. solution of sodium chloride, and one gram of potassium chloride in 100 grams of water makes a one per cent. solution of potassium chloride. But it is incorrect to regard these two solutions as being of equal concentration, for they contain unequal numbers of molecules. It is more useful and rational to compare solutions containing the same number of molecules. The molecular weight of sodium chloride equals 58·36; that of potassium equals 74·14. If now we dissolve 58·36 grams of sodium chloride in one litre of water, and 74·14 grams of potassium chloride in the same volume of water, we get equi-molecular solutions. We call these normal solutions. Such normal solutions of sodium chloride and potassium chloride are more nearly comparable in their physico-chemical properties, such as osmotic pressure and electrical conductivity, than solutions containing, say, 58·36 grams or 74·14 grams each of potassium chloride or sodium chloride.

It is desirable for you to remember the fact that the electrolytic dissociation by which the molecules of a soluble salt or acid partly split up into ions increases as the solution becomes more dilute. Calculations show that a normal solution of hydrochloric acid has 75 per cent. of its molecules in the dissociated state, while a tenth normal solution contains 86 per cent., and a one-thousandth normal solution

contains 98 per cent. of dissociated molecules. There are two unmistakable evidences of this increasing dissociation. One of them is the increase in the power in the solution to conduct electricity, the other is a relative increase in the osmotic pressure or power of the substance in solution to pass through permeable membranes. Now, since we know that the electrolytic conductivity and the osmotic pressure both increase proportionately to the number of molecules in a solution, we are justified in assuming that when a molecule is dissociated the ions into which it separates have the value of molecules with respect to these physical phenomena.

There are many substances in the animal body which undergo no electrolytic dissociation. This is the case, for example, with proteid substances like serum albumin and serum globulin. It is also true of sugar. In a solution of sugar the osmotic pressure increases directly with the concentration and temperature of the solution. The inorganic salts and acids apparently break this law, but it has been shown conclusively that these apparent exceptions are due to the electrolytic dissociation of these bodies in consequence of which the ions take on the physical behaviour of molecules.

It may possibly appear to you that the laws relating to electrolytic dissociation and osmotic pressure are foreign to the subject of pathological chemistry, but this is certainly not the case. Whenever two fluids come in contact, either directly or indirectly, through a semi-permeable membrane, the laws of osmotic pressure come into action. Now these simple conditions exist in nearly all parts of the animal body. We may therefore say that we cannot conceive of any physiological or pathological process in the living organism in which osmotic laws do not play a part. How these laws operate we do not yet fully understand, but we may safely say that the knowledge already gained helps us to understand some processes which would otherwise be less intelligible.

Let us take the chief inorganic salts of the food and consider their more important physiological and pathological relations without losing sight of the physical phenomena to which I have referred.

It will be convenient to consider, first, the food salts and their absorption in the digestive tube, and, secondly, the salts of the blood plasma in their relation to the nutrition of the tissues, to the excretion, &c.

The chlorides of sodium and potassium constitute the major part of the salts in the dietary of the human subject, an adult taking not far from 8 grams of sodium chloride daily and 4 grams of potassium chloride. Although these two salts resemble each other in many of their properties, it is perhaps best to speak of sodium chloride separately.

Sodium chloride possesses physico-chemical properties which aid us in understanding its action in the body. Its molecular weight being small (sodium 23, chlorine 35·37, sodium chloride 58·37), the osmotic pressure exerted by its solution is greater than that of any other food salt, taken weight for weight, because each gramme contains a larger number of molecules. Another important property is that it dissociates very readily into its chlorine and sodium ions. This dissociation further enhances its osmotic pressure, which is probably the main action of sodium chloride in the body. The ions of many salts exhibit activities which may be described as specific, but this cannot be said to be true of sodium chloride. The sodium and chlorine ions are ordinary and essential constituents of all the body fluids, and the cells generally are accustomed to their presence. The presence of these ions in greater or lesser concentration induces alterations in the physical characters of the blood and lymph, and urine, and digestive juices. Otherwise the chlorine and sodium ions are to be regarded as indifferent to the cells of the body.

You are of course conversant with the fact that when two solutions of salt are separated by a permeable membrane in such a way as to prevent ordinary filtration, there occurs a constant interchange of the salts and the fluids until the concentration of the molecules, and hence the osmotic pressure, is equal on the two sides of the membrane. When the molecular concentration on the two sides of the membrane has become the same, the solutions are isotonic. The more concentrated solution is hyperisotonic. The weaker one is hypisotonic. Osmotic processes play an extremely important part in facilitating the movement of fluids and the diffusion of salts in the organism, and no salt has so active a part in determining osmosis as sodium chloride. The epithelial cells of the mucous membranes and the endothelial cells of the smaller vessels act as permeable membranes through which mineral salts are constantly passing, partly through the agency of osmotic pressure.

Although the absorption from the stomach and intestine of sodium chloride, and of soluble salts generally, is helped by the agency of osmotic pressure, it is clear that this absorption cannot be fully explained by any purely physical forces at present known. Thus, if we introduce into the stomach a salt solution which is isotonic with the blood plasma, the fluid and the salt are absorbed notwithstanding the equality in osmotic pressure on the two sides of the epithelial lining of the stomach. This is because the cells exert a so-called 'vital' action in taking up the fluid and the salt ions quite distinct from any physical influences at present known to us. If now we introduce into the intestine a hypisotonic solution, it is even more rapidly absorbed, because the osmotic pressure is exerted in the direction of the blood and aids the vital action of the epithelia. But if we place a hyperisotonic solution in the digestive tube, the osmotic flow is in opposition to the direction of the epithelial activity, and for a time water may be extracted from the blood. This abstraction of water is a feature of many cathartic salts which are used in concentrated form.

The conditions attending the absorption of potassium chloride are very similar to those which relate to sodium chloride, although the larger size of its molecule makes the osmotic pressure of this salt lower. When the two chlorides reach the blood they part company to a considerable extent, as is shown by the fact that the potassium ions preponderate in many of the body cells, while the sodium ions are present in greater concentration in the blood and lymph where their osmotic activities are of the highest importance.

Besides the chlorides of which I have just spoken, we have to consider the carbonates, the sulphates, and phosphates introduced with the food. The carbonates are not ordinarily taken into the stomach in considerable amount, and of this moderate quantity only a small portion is absorbed as carbonate owing to the conversion into chloride which is effected by the hydrochloric acid of the gastric juice. The sodium and potassium carbonates are readily soluble and bland to the mucous membrane of the stomach and intestine. So far as we are aware the carbonates of sodium, potassium, calcium, and magnesium have little local effect on the mucous membrane of the digestive tract. Thus you see that salts with the acid ions Cl and CO_3 are relatively indifferent as regards local effects. With the acid

ions of the sulphates the case is different. The SO_4 ions occur in the solutions of the sodium, potassium, and magnesium salts (Na_2SO_4, K_2SO_4, $MgSO_4$), and it is noticeable that all these bodies have strong cathartic effects in concentrated solution. This irritant action can be referred only to the SO_4 ions, since the same basic ions in combination with other acid ions do not exhibit this effect.

In connection with the irritant action of the SO_4 ions it is interesting to observe that in a series of soluble salts with the same acid ions, those salts have the greatest physiological activity that have the lowest molecular weight, *i.e.* that contain the greatest relative proportion of acid ions. Thus 7·4 grams K_2SO_4 with a molecular weight of 174 contains 4·1 grams SO_4; 7·4 grams of $Na_2SO_4+10H_2O$, with the molecular weight of 321, contains 2·2 grams SO_4; 7·4 grams of $MgSO_4,6H_2O$, with the molecular weight of 228, contains 3·2 grams of SO_4. Now in case the cathartic action of these salts depended on the SO_4 ions we should expect potassium sulphate to act more energetically than an equal weight of sodium sulphate or of magnesium sulphate. This is in fact the case. The salt calcium sulphate, being largely insoluble, cannot be compared with the other sulphates that have been mentioned.

The salts of H_3PO_4 (ortho-phosphoric acid) in the food are chiefly those of calcium, though the more soluble sodium and potassium phosphates are also ingested. Calcium phosphates occur as the primary $CaH_4(PO_4)_2$, the secondary $CaHPO_4$ and tertiary $Ca_3(PO_4)_2$. The primary salt is the only one that is moderately soluble in water. Hence very little calcium is absorbed from the digestive tract as phosphates. The tertiary phosphate occurs in the ash of milk, having been previously in combination with casein. It is also present in meat. It is still a question whether calcium phosphate is absorbed from the intestine. The phosphoric acid ions (PO_4) must be absorbed chiefly in combination with sodium and potassium, but even in this form the absorption must be slight. The PO_4 ions resemble those of SO_4 in being irritant and cathartic in action when present in strong medicinal solutions.

The absorption of calcium salts is a matter of the first importance for the growth and maintenance of the skeleton. The chlorides and carbonates of calcium are to some extent taken up from the digestive tract, but, as I have just said,

we do not know whether it is true of the phosphates. Anything which leads to a prolonged and impaired absorption of calcium results in a modification of the skeleton, which, as you know, contains a very large proportion of calcium and magnesium phosphates. It is easy to show experimentally that the growth of the bones is very much restricted in young animals when the lime salts of the food are deficient. But although the bones are quantitatively imperfectly developed under these circumstances I have found that their composition differs little from that of normal bone. It has been claimed that the deprivation of lime salts in the food is the cause of rickets. This contention has not been successfully sustained. In rickets there is impaired growth of bone containing a diminished proportion of lime, but it is highly improbable that the mere reduction of the calcium of the food, or a diminished absorption of such salts, suffices to produce the characteristic lesions of rickets.

We have, indeed, no reason to suppose that the capacity of the intestinal epithelium to absorb lime is always reduced, since rickety children to whom calcium salts were administered showed as large an increase in the excretion of lime by the urine as did normal children under similar conditions.

In thinking of the relationship of rickets to the calcium phosphate in the blood, one cannot help doubting whether the presence of a normal quantity of calcium in the blood assures its normal utilisation by the bones. There are in fact recent observations which show that in rickets the liver, kidney, spleen, heart, and central nervous system contain as much calcium as in health. One is thus led to suspect that in a case of rickets there may be peculiarities in the activities of the bone cells which modify their capacity to utilise the salts of calcium. I hope to discuss this subject with you at greater length in connection with the chemical pathology of the bones.

Having now reviewed some features of the absorption of the mineral ingredients of food, let us consider certain relations of the salts in the blood in health and disease.

The plasma of the blood contains inorganic salts which are partly present in a free state, partly in combination with the proteid elements of the blood. Thus sodium chloride, the most important abundant salt of the blood, exists as such; but the calcium phosphate must be combined with the

proteid of the blood or it could not remain in solution. The human plasma holds in solution salts of sodium, potassium, magnesium, and calcium. These salts are chiefly present as chlorides and phosphates in a state of electrolytic dissociation. Now it is known that in health the molecular concentration of the serum, that is, the total number of molecules in a given volume, is nearly constant. This is shown by the fact that the freezing-point of the blood is regularly 0°·56 C. below the freezing-point of water. Moreover the concentration of the serum in organic molecules is nearly constant. Again, the molecules which contain chlorine constitute a large and very nearly constant part of the total electrolytes in solution, that is, of the ions conducting electricity. The chlorine content varies little from 0·58 per cent. of sodium chloride, and it is chiefly on this high content of sodium chloride that the osmotic pressure of the blood depends.

The constancy in the concentration of the inorganic and organic molecules of the blood, notwithstanding the continual accessions of new material and the constant removal of other material, is a remarkable thing. It shows us plainly that a highly complex regulatory mechanism is at work, involving the control of various physiological processes. Among these are the absorption from the digestive tract, the excretion of water by the skin and lungs, the exchange of material between the tissue cells and the blood, and, lastly, the excretion of superfluous molecules in watery solution by way of the kidneys. Through the union of these various factors the osmotic pressure of the blood is maintained at a nearly constant level. This constancy in osmotic pressure appears to be a necessary element in the normal life activities of the cells. The importance of the osmotic pressure of the plasma for one class of cells, the red cells of the blood, is shown by the fluctuations in the volume and water content of these cells with the osmotic pressure of the plasma. You know that any considerable reduction in the molecular concentration of the plasma is followed by a swelling and disruption of red blood cells. There is good reason to believe that a similar sensitiveness to the state of the molecular concentration of the blood exists in the case of the different kinds of cells bathed by the plasma.

Now since the osmotic pressure of the blood depends on

the molecular concentration, and this concentration in turn depends largely on the salts in the plasma, you can readily appreciate the very great importance of the inorganic salts for the maintenance of the physico-chemical conditions that underlie metabolic processes. These inorganic salts are operative chiefly through their dissociated molecules or ions.

The presence of the ions in the blood and other fluids of the body explains the ability of the tissues to transmit electricity. The organic material of the body cannot conduct electricity. But since there is little doubt that the partial conversion of caloric energy into electrical energy is a necessary incident of life, we see here another evidence of the essential character of ion action. How important this ion action may be to the carrying on of oxidations in the cells we do not yet understand.

I have now said enough to emphasise the physiological importance of the salts both in the blood and in the organism generally. You will naturally ask where these physiological facts find application to disease. It will be a long time before anything like a satisfactory answer can be given to this question. The conditions are far too intricate for our present understanding. Some things of practical and theoretical importance to us as physicians have, however, come to light in connection with the behaviour of the mineral salts in relation to disease, and to these I now invite your attention.

It will be convenient to consider in turn the chlorides of sodium and potassium, the sodium carbonates and phosphates, and the salts of calcium. Sodium chloride, the most abundant salt of the food, enters the body in the large amount of 5 to 12 grams daily, and is excreted in a nearly equally large amount by the urine. A reduction in the salt income is rapidly followed by a corresponding reductiom in excretion, *e.g.* the body holds its salts in such a way as to maintain nearly the normal concentration in the serum, even in starvation. A marked fall in the salt of the food is followed by defective absorption of the food-stuffs. Therefore you must see to it that your patients receive sufficient salt. It is an old observation that salt deprivation in cattle is followed by impaired nutrition. The same is true in man. As a rule you can easily tell from the urine of your patients if they are receiving too little salt.

While in health the administration of sodium chloride is

promptly followed by an increased output of chlorine nearly or quite equal to the quantity of salt taken.

This is not the case in some forms of disease. Thus in marked anæmias and acute fevers it has been found that the organism retains chlorine in considerable amount when administered in addition to the food. In the case of chlorosis the retention of chlorine is said to be greater than in pernicious anæmias. The most satisfactory explanation of the retention is that it depends on the relative excess of water in the blood. According to this view the administration of sodium chloride is followed by a smaller sodium chloride excretion than should occur in health, simply because the chlorine is held in the blood to compensate a deficiency in concentration. In the case of pneumonia the retention of sodium chloride in the body is pronounced. Give 1 gram of chlorine daily and the urine of the pneumonia patient will contain, say, 0·5 gram; give 8 grams daily and you get from 2 to 3 grams of chlorine in the urine. This, you see, represents a considerable retention of chlorine, and chiefly chlorine combined with sodium. What is the cause of this retention of chlorides? The most reasonable explanation is that the chlorine retention is due largely to a watery condition of the blood during fever, in which sodium chloride is held back from the organism for the purpose of maintaining the molecular concentration of the blood in ions at nearly the normal level. This explanation applies equally well to the retention of sodium chloride which occurs generally during fever. We may picture to ourselves that in fever there is a flow of water and salts from the blood to the tissues, while during convalescence the water and salts return into the blood. During the febrile period the water and chlorine of the urine are much diminished; after the fever they increase.

There is a second important influence, in the case of pneumonia, which favours the retention of chlorine. This is the existence of a considerable exudate into the alveoli of the lung. I think these influences account for the great reduction of the chlorides in the urine with which we meet in many cases of pneumonia.

In connection with the retention of chlorine in pneumonia I wish to call your attention to the behaviour of the phosphates, because it illustrates the tenacity with which the organism holds its salts when the concentration of the blood is lowered.

It is well known that in pneumonia, as in fever generally, the excretion of phosphates is increased in absolute amount, as compared with the non-febrile state. Nevertheless the amount excreted is not so large in proportion to the excretion of nitrogen as one would expect from the relations of the phosphorus and nitrogen content in the food. The ratio of nitrogen to phosphorus during fever is 20 or 10 to 1, when we should expect it to be about 6 to 1. Thus the blood is holding back phosphorus just as it holds back chlorine. The explanation appears to be that the chlorides retained do not suffice to maintain the normal concentration of the fluids of the body, and that hence the phosphates which are easily soluble are kept back to help in the maintenance of this concentration. But please note what happens when we give the patient an abundance of sodium chloride. If we add an abundance of sodium chloride to the food, the phosphates in the urine are so much increased that the ratio of nitrogen to phosphorus becomes about 6 to 1. In other words, an increased concentration of the blood in chlorides permits a prompt increase in the excretion of phosphates.

The molecular concentration of the blood in sodium chloride corresponds closely to that of various normal and pathological exudates and transudates. Thus the percentage of sodium chloride in the lymph, in the aqueous humour, in the fluid of œdema, and in the exudate of pleurisy and hydrocele is never far from six tenths of one per cent., *i.e.* almost the same as that of the blood. This correspondence points to the *rôle* played by the osmotic pressure of the dissociated molecules of sodium chloride in the blood. The passage of sodium chloride into large exudates tends to lower somewhat the concentration of sodium chloride in the blood. Hence the sodium chloride of the blood is greedily retained by the blood in compensation of the loss. The result is a diminution of the sodium chloride in the urine. *Per contra*, when the absorption of exudate holding salt takes place, the chlorine in the urine is increased. The transudation of salt is a requisite of every pathological exudate and transudate.

The sodium chloride of the blood stands in very close and important relationship to the activities of two kinds of epithelial cells, namely, those of the stomach and those of the kidney. You know that the stomach of an adult human being secretes a very considerable amount of gastric juice in the course of twenty-four hours, and that this gastric juice

brings with it many grammes of hydrochloric acid. Now there is no reasonable ground to doubt that this hydrochloric acid comes from the sodium chloride of the blood. The most intelligible conception of the process of secretion involves the view that the gastric cells take sodium and chlorine ions from the blood, and through some obscure activity, which we find it convenient to call vital, bring about a conversion of the chlorine ions into hydrochloric acid and of the sodium ions into sodium carbonate.

The chemical interchange is represented by the following equation:—

$$ClZNa + H_2O = ClZH + NaZOH.$$

The sodium hydroxide is probably converted promptly into sodium carbonate by the carbonic acid of the blood. The stream of hydrochloric acid is always directed into the stomach, while the simultaneously formed sodium hydroxide or carbonate passes towards the blood and lymph. At least a portion of the alkaline sodium carbonate which is thus added to the blood is probably utilised in conferring the normal alkaline reaction on the pancreatic juice, the succus entericus, and the saliva. As yet we cannot see deeply enough into the chemistry of nutrition to recognise the consequences to the organism that may accrue from the impaired secretion of the hydrochloric acid of the gastric juice. But I wish to suggest that a chronic state of defective secretion of this acid very probably entails other consequences than those which can be referred to impaired gastric digestion, namely, nutritional disturbances connected with diminished alkalescence of the pancreatic and other important secretions.

Since the secretion of free hydrochloric acid by the epithelial cells of the stomach is so closely connected with the sodium chloride of the blood, one might perhaps expect to find this secretion impaired in cases where the chlorine content of the blood is low. In fever, in anæmia, and in starvation we find that the administration of chlorides is followed by a considerable retention of chlorine in the body, and we are doubtless justified in making the inference that the blood in these states is poor in sodium and chlorine ions. We know also that in fever, in anæmia, and in starvation the free hydrochloric acid is diminished markedly. Perhaps the diminution must be referred largely to interference with the functions of the secreting epithelial cells of

the stomach. But we may at least suspect that the deficiency of chlorine ions in the blood is also a factor.

Let me now speak of the relation of sodium chloride to the renal epithelium. You are aware that if we add to the ordinary food of a healthy man a considerable quantity of sodium chloride, this sodium chloride appears promptly in the urine. The organism does not retain chlorine because it already has enough for its needs. The kidney seems to be entrusted with the important function of maintaining a normal percentage of chlorine in the blood. When the blood grows poor in chlorine, the sodium and chlorine ions in the blood no longer pass into the urine. The work of the kidney thus appears to be at least roughly proportional to the concentration of the chlorine and sodium ions in the blood. Doubtless the high osmotic pressure of the salt has to do with its ready elimination; yet we have good reason to suppose that the process of elimination is by no means purely a physical one, but involves the so-called vital activities of the renal epithelium.

If we infuse into the circulation of a dog a concentrated solution of sodium chloride, the kidney is soon stimulated to active diuresis; that is to say, removal of the excess of salt from the blood by the kidney entails the removal of a considerable volume of water. This volume of water may be greatly in excess of the water which was infused. Now this diuretic action of common salt is one which we can put to practical use. If you introduce a hot salt solution into the colon of a patient with uræmia or with kidneys which have ceased their normal activity owing to shock, you will generally be gratified by the promptness with which the flow of urine is re-established. In such instances you not merely cause the slumbering renal epithelium to excrete the salt and water which you have introduced, but, as I have shown by numerous experiments in animals and observations on man, you also stimulate the excretion of urea and other substances that have been retained in the blood. I advise you to employ a solution of about 1 per cent. of sodium chloride. Such a solution, having a greater concentration in chlorine and sodium ions than the blood itself, would draw water from the blood were only physical processes in play. The intestinal epithelium, however, takes up the salt and water promptly.

The potassium of the food occurs partly in union with

chlorine, partly with phosphoric acid, and is especially abundant in vegetable food. The potassium salts, readily dissociated and easily absorbed, find their their way into the urine as promptly as the salts of sodium. This absorption is not, however, so complete as that of the sodium salts, and a small amount can always be found in the fæces. On passing from the digestive tract into the blood the potassium ions required by the tissues are quickly taken up, and any excess of such ions above the normal content of the blood is quickly eliminated by the kidneys. In the blood the low content of potassium ions is in striking contrast to the concentration of sodium ions, whereas, in many of the cells, this quantitative relation is reversed. This is noticeable in the red blood cells of man and in the muscles of mammals generally. There are at least two reasons why a high potassium content for the blood is less adapted for the needs of the body than a high sodium content. One is that the potassium salts are highly toxic to the nervous system and heart. The other is that the molecule of potassium chloride being larger than the molecule of sodium chloride, the salt exerts a considerably lower osmotic pressure, weight for weight, than sodium chloride.

While the potassium ions in concentration induce paralysis of the heart, in the moderate concentration in which they exist in the body they furnish an important stimulus to rhythmic cardiac contractions and relaxations. The potassium ions probably exert this effect by entering into combination with the living protoplasm of the muscle. It seems not unlikely that potassium has a similar stimulating action on the skeletal muscles.

At present we do not know much about the behaviour of the potassium ions of the organism in disease. In fever the potassium like the sodium chloride is closely held by the tissues, and the administration of potassium chloride is followed by some retention. The reasons for this retention are of the same nature as those which I mentioned in connection with sodium chloride. In acute starvation and chronic inanition the organism holds its sodium choloride more jealously than its potassium salt; hence the urine may contain more potassium ions than sodium ions, contrary to normal conditions. Where the kidney shows insufficiency in the excretion of urea there may also be difficulty in excreting potassium ions. Hence, in certain uræmic states, the

potassium content of the blood is increased. The increase is moderate, never great. Nevertheless an entire volume and several monographs have been written to prove that the potassium salts are the cause of the toxic symptoms of uræmia. This position is untenable. Still it is possible that the excess of potassium ions in the blood is sufficient to contribute to the production of uræmic symptoms in some instances of renal disease.

Let us now consider for a moment the fate of the salts of the alkali earth metals in the body. While calcium is present both in animal and vegetable food, it is, like potassium, especially abundant in the latter. By no means all the calcium exists in the inorganic state as salts of phosphoric and carbonic acids. A portion is united to organic materials such as casein, the proteids of the egg yolk, and certain seeds; a fact to be remembered in prescribing a diet rich in calcium. There is good experimental evidence that both the organic and inorganic calcium compounds undergo resorption and reappear in the urine. But this resorption is probably not very large. We know that only five to ten per cent. of the calcium in the food is excreted in the urine. This fact might very readily lead us to underestimate the extent of calcium absorption. It may surprise you to learn that the excretory path for calcium is not the kidneys, but the epithelium of the intestine. It is by way of the succus entericus that calcium normally leaves the body; therefore it is not permissible to estimate the proportion of calcium that has actually been absorbed from a study either of the urine or of the fæces.

The calcium of the blood, though present there in small amount, performs important though not fully understood functions. I have not now in mind the utilisation of the calcium of the blood, in the construction and maintenance of the skeleton, but functions of quite a different character. I refer to the influence of calcium on the cardiac muscle and also to its relation to the coagulation of the blood.

In speaking of the action of the potassium salts of the blood I drew your attention to the effect of these basic ions on the rhythmic contractions and relaxations of the heart. The calcium ions, though apparently as essential to the maintenance of cardiac activity as the potassium ions, exert a somewhat different influence, since they supply the stimulus to a prolonged contraction with delayed relaxation. In the

frog, at least, the action of the calcium and potassium ions in the heart is antagonistic. It is a very interesting fact that the voluntary muscles also are favourably influenced to contraction through the presence of calcium ions, even in small concentration. At the present time, however, it is impossible to say whether pathological conditions arise in the voluntary and involuntary muscles as the result of deficiency in calcium salts.

If we draw blood from a living animal and add to it a small amount of oxalic acid, the blood fails to coagulate. This is because the acid precipitates the calcium as oxalate of lime, and thus deprives the blood of ions which play a part in the process of coagulation. Just how the calcium acts in favouring coagulation has been the subject of considerable controversy. It has been shown that the calcium ions are not necessary for the activity of the fibrin ferment when this has been formed, but that this fibrin ferment cannot develop from prothrombin, the antecedent of this ferment in the circulating blood, without the presence of calcium. It has been suggested that calcium salts be used therapeutically in conditions of disease where it is desirable to increase the coagulability of the blood, as in bleeders and persons with large aneurysmal dilatations. It is even claimed that some favourable results have been obtained in this way. But this suggestion appears no more rational than the treatment of rickets with calcium salts, because there is no evidence of a deficiency in the calcium ions of the blood in any of these pathological conditions.

An interesting phenomenon in which the calcium salts play a part is the process of calcification in the blood vessels, in the lungs, and in many tumours. We are ignorant of the conditions that determine the occurrence of a deposit of calcium salts in tissues normally free from such deposits, but there is very good reason to think that injury to the tissues is a necessary antecedent to pathological calcification.

We do not as yet know much about conditions in which the excretion of the calcium ions is pathological. A retention of calcium in the organism has been observed in some febrile conditions—a retention apparently comparable to that noted in the case of the chlorine ions of which I have already spoken. I can offer you no explanation of this retention which appears to me satisfactory.

An absolute loss of calcium by the urine and fæces has been noted in pernicious anæmias and in some cases of diabetes. In the case of pernicious anæmias the excretion is associated with a retention of chlorine in the body. In diabetes the loss of calcium is dependent on the presence of an acid intoxication. I explained to you in the lecture on the chemical defences of the organism against disease that the bases ammonium, sodium, potassium, and calcium are all called upon in some cases of diabetes to aid in neutralising and removing organic acids, probably chiefly oxybutyric acid, from the body. The removal of calcium indicates that the alkali resources of the body have been nearly exhausted, and is thus an evil omen. The calcium which is sacrificed has so small a basic value that it is incompetent to delay materially the fatal issue of the acid intoxication. The loss is, however, one which in some instances greatly impairs the strength of the bones. I regret that I cannot tell you what interpretation to give to the calcium loss in pernicious anæmias. The loss appears to be constantly observed, and possibly it is the expression of an intoxication by acid as in diabetes; but I know of no facts in support of this suggestion.

I am able to tell you even less about magnesium than about calcium. The magnesium of the food, like the calcium, occurs chiefly as a phosphate, but this phosphate is somewhat more readily soluble, and hence better adapted for absorption. It is thought that a small amount of the magnesium that has been absorbed is excreted by the succus entericus, as in the case of calcium. We know almost nothing of the *rôle* of the magnesium in the normal or in the disturbed processes of life, yet its occurrence in the blood in nearly the same concentration as the calcium ions and its presence in protoplasm indicate that magnesium performs a not unimportant part in the organism. In one function at least the magnesium differs strikingly from calcium. The ash of bone contains nearly 40 per cent. of calcium, which must thus be regarded as the mineral basis of the skeleton. On the other hand the bones contain less than one per cent. of magnesium.

As I shall indicate more fully when I speak of the pathological chemistry of starvation, the urine contains much more calcium than magnesium when the food supply is withheld. This is in contrast to what happens on an

ordinary mixed diet, although it is by no means a constant phenomenon to find the magnesium of the urine in excess of the calcium. The explanation of the relative increase of calcium in starvation is that the food contains considerably more magnesium than calcium.

An interesting fact in regard to the action of the magnesium ions on protoplasm has recently come to light through the experiments of Loeb of Chicago. This investigator found only one way in which it was possible to stimulate the unfertilised egg of a sea-urchin (by means of mineral salts) so that it will develop into a larva. This was by treating the unfertilised egg with a mixture of almost equal parts of sea water and a $\frac{2}{8}$ normal solution of magnesium chloride. This remarkable stimulus to segmentation of the egg must be attributed chiefly to the stimulating action of the magnesium ions. I mention the observation to you, not as being of medical significance, but because it illustrates a notable physiological property of the magnesium ions that may serve to increase your appreciation of the importance of the mineral elements of the body. We may some day find that the magnesium ions are of the highest importance to the maintenance of certain life activities in the cells of the human body.

I have already alluded to some of the conditions attending the absorption of the phosphates and sulphates from the intestine. Let me now say something about the phosphate and sulphate ions of the blood and their destination. The phosphoric acid of the blood is present there in only small amount, partly in union with calcium and partly in combination with sodium and perhaps potassium. The calcium phosphate comes from the food, and is utilised chiefly in the formation of bone. The phosphoric acid united to the sodium and potassium of the blood may come in part from the food, but there is another important source of this phosphoric acid which you must not overlook. This is the oxidation of the phosphorus-holding cells of the body in the course of metabolism. The phosphoric acid thus formed probably gives rise to the disodium phosphate of the blood, Na_2HPO_4. It is, of course, impossible that the blood should contain either free phosphoric acid or its acid salt NaH_2PO_4, the monosodium phosphate. Nevertheless the urine contains the monosodium salt of phosphoric acid, to which its acid reaction is partly due. How are we to explain the remarkable

fact that the alkaline blood which circulates through the kidney is the mother of an acid urine? No explanation is possible that fails to take account of a specific activity on the part of the renal epithelium, an activity comparable to that by which the gastric cells free the Cl ions from their sodium base and pass them into the cavity of the stomach. We may assume that the blood passing to the kidney contains carbonic acid and disodium phosphate.

$$\begin{array}{ccc} \text{OH} & & \text{ONa} \\ \text{CO} & + & \text{POONa} = \\ \text{OH} & & \text{OH} \end{array}$$

Carbonic acid. Disodium phosphate.

and that the renal epithelium effects a rearrangement of ions by which there result monosodium phosphate and sodium bicarbonate.

$$\begin{array}{ccc} \text{ONa} & & \text{ONa} \\ \text{POOH} & + & \text{CO} \\ \text{OH} & & \text{OH} \end{array}$$

Monosodium phosphate. Monosodium carbonate (sodium bicarbonate).

The acid salt NaH_2PO_4 passes into the urine, and the alkaline salt $NaHCO_3$ is returned to the blood, thus completing the analogy with the action of the gastric epithelium, which returns an alkaline salt to the blood.

The acidity of the urine is thus influenced by the disodium phosphate of the blood and by a specific activity of the renal cells. We are, however, in the dark as to the details of the process, and at present cannot give a satisfactory explanation of all the fluctuations in acidity of the urine which depend on differences in the content of the acid sodium phosphate. In urines that are neutral when passed the phosphoric acid is probably present as the disodium salt; in acid urine the hydrogen ions of the monosodium phosphate are also present.

It is customary to speak of the acid sodium phosphate as if it were alone responsible for the acidity of the urine. This is surely an error, because other acid salts are quite as likely to be concerned. Thus, the sulphuric acid in the urine is capable of forming acid salts, as, for instance, the acid sodium sulphate. If now we have a solution like the urine, which contains phosphoric and sulphuric acid in

excess of the amount required to form neutral salts of sodium and potassium, we know that the solution contains ions of potassium and sodium, ions of SO_4 and PO_4 and ions of H. We cannot say in what proportion the different basic ions belong to the acid ions, since all are in the dissociated state, and we have quite as much right to assume the presence of acid salts of sulphuric acid as acid salts of phosphoric acid in an acid urine. You will further realise the justice of taking account of the sulphuric acid of the urine as a maker of acid salts when I remind you of the fact that, on a mixed diet, the healthy adult has almost as much sulphuric acid in the urine as phosphoric acid.

Probably you are all familiar with the term 'phosphaturia,' but very likely you have not a very clear conception of what it means. Whenever there occurs a spontaneous separation of the earthy phosphates, that is, the calcium and magnesium phosphates of the urine, custom justifies us in saying that we have to deal with phosphaturia. If you make use of the word in this sense, and with a full recognition of the fact that a separation of phosphates is liable to occur from any concentrated urine that is neutral in reaction, there is no objection to the use of the term. But if you infer that a separation of phosphates means that there is a pathological increase in the excretion of the earthy phosphates you will be giving a wrong interpretation to phosphaturia. Please remember that it is a difficult matter to state what constitutes an excessive excretion of earthy phosphates, and that in most cases of phosphaturia there is no evidence of any such excess. I believe I shall not mislead you by saying that the chief pathological significance of the separation of phosphates is the neutral state of the urine which permits this separation. Still there are instances in which the excretion of phosphates is regularly in excess of the normal output. On this subject I shall speak to you again when we discuss the pathological chemistry of certain forms of nervous disease.

A few minutes ago I told you that the urine contained sulphuric acid in an amount nearly equal to that of phosphoric acid—that is, from 1 to 3 grams daily. Nevertheless the blood contains SO_4 ions only in very small concentration—about one twentieth the concentration of the urine in SO_4 ions. In this contrast between the SO_4 ions in the blood and urine there is a resemblance to the contrast of

the urea content of the blood and urine. In each instance the blood contains something which is of little use to the organism, something which produces toxic effects unless it is promptly removed by the action of the kidneys.

The SO_4 ions of the blood come only in part from the food, which contains very small quantities of sulphates. The greater part of the SO_4 comes from the oxidation of sulphur in the course of the metabolism of the cells of the body. While the sulphur ions exist in abundance in the salts of certain connective tissue structures, such as cartilage, they are to be regarded chiefly as excretory products of oxidation.

I shall now recapitulate with respect to the more important facts about the different salts in the food and their destination in the organism. We have seen that the chlorides are the salts most abundant in the food, in the blood, and in the urine, and that the action of the sodium and chlorine ions is mainly a physical one connected with their osmotic pressure. We have also seen that while the sodium and chlorine ions travel rapidly through the body in the performance of their physical functions the cells and fluids of the body hold their ions jealously, and guard against any marked fall in the normal concentration of the blood. Consequently we observe a great reduction in the chlorine of the urine when the chlorides of the food are reduced, and similarly a detention of chlorine in the body when there is an accumulation of fluid in the organism, as in fever and certain anæmias.

In the sharpest contrast to the chlorides of sodium and potassium stand the calcium phosphates. The large molecules of the calcium salts, their slight dissociation and low osmotic pressure, lead us to expect wholly different physiological properties from those that belong to the chlorides of the alkalis. And such differences indeed exist. These calcium salts, difficult of absorption and present in small concentration in the blood plasma, play almost no part in the osmotic changes in the cells and nutrient fluids. They form the mineral basis of the skeleton, and conditions which prevent their deposition in the bones are concerned with the development of rickets and osteomalacia. The slow metabolism and relative permanence of the bony framework of the body are reflected in the small calcium excretion of the urine, just as the intense activity and rapid replacement of the chlorides may be inferred from the large chlorine content

of the urine. The salts of magnesium stand close to the calcium salts in respect to their physico-chemical properties. Of their significance we understand little at present, but what we know of the influence of the calcium salts upon coagulation and upon the irritability of muscle leads us to infer that the presence of the magnesium ions in the blood is important to the maintenance of vital processes. We are also in the dark as to the part played by the potassium ions, though, as already stated, the potassium chloride presents many analogies to sodium chloride. There is reason to think, however, that the excessive accumulation of potassium ions is sometimes a factor in the production of toxic symptoms.

While I have tried to impress on you the great importance of the physico-chemical properties of salts, especially in relation to their capacity to permeate the cell structures of the body, it has been my wish to make you realise that other influences of a so-called 'vital' character are intimately associated with the passage of the salts through the organism. We nowhere see more clearly the evidences of the vital activity of the cells than in the differences in the urine and blood in respect to the concentration of their mineral ions. If the osmotic pressure and diffusion of the mineral ions in the blood were the only factors in determining the passage of these ions into the urine, we should expect to find the concentration of the salts in the blood and urine very nearly equal. What we actually find is that the blood contains sodium, potassium, and chlorine in greater concentration than in the urine, while, on the other hand, the urine is richer in calcium and magnesium and sulphuric acid. Such conditions can only result from the specific 'vital' activity of the renal cells.

In the few minutes that remain to us this morning I wish to speak to you of some of the effects of the drinking of mineral waters. When you reflect how extensive is the internal use of such waters, not only at the various spas of this country and of Europe, but also in an indiscriminate way without medical direction, you can hardly fail to see that the subject is one well worthy of your attention.

The effect of a mineral water upon a given individual naturally depends on a number of factors, of which the more prominent are the condition of the subject, the character of the salts dissolved in the water and their

concentration, the presence or absence of free carbon dioxide in solution, the quantity of water used, and the period of time through which the use of the water extends. Whereas I cannot speak of these factors in detail, perhaps it is possible to show you that they have all to be taken into consideration in giving advice to patients. Carbonated waters are popular for table use, and by many persons are preferred to those which are still. It has very likely occurred to you to ask if it is a matter of indifference to the body whether a drinking water is or is not highly charged with carbon dioxide. I regret to say that I cannot inform you as accurately as I could wish with regard to the advantages and drawbacks attending the use of highly charged waters. The subject is one that deserves more attention than it has received. I cannot say much in favour of carbonated waters except that they are palatable to many persons, and sometimes relieve nausea. Whether the carbon dioxide ever has a distinct effect on the quantity and quality of the gastric juice I do not know. It is claimed that the gas stimulates the gastric secretion. On the other hand, there is little doubt in my mind that the constant use of carbonated waters is sometimes harmful in several ways, as through local irritant action or through an accumulation of gas in the stomach favourable to the production of atony. Whether there are other detrimental effects of a more indirect nature I cannot say. I can tell you from personal experience that the introduction of large volumes of carbon dioxide into the stomach and intestine is quickly followed, in the case of dogs, by a decided alteration in the reaction of the urine. The acid urine becomes rapidly neutral or alkaline. One would hardly expect so decided a result in the human subject simply from carbonated water, but it is possible that there is some influence on the reaction of the urine. Clinical experience indicates that there are some persons in whom uric acid calculi are more rapidly formed where carbonated waters are used than when still waters are used; but I have no explanation of the fact, and do not know under what circumstances such an effect is likely to be noted.

The nature and concentration of the salts contained in a mineral water are of course leading factors in determining its action. Most natural mineral waters act chiefly in one of two ways; namely, by their passage through the organism after absorption or by the irritant action of their

ions on the digestive tract, which prevents any considerable absorption and favours catharsis. These two types of waters are represented in the Kissengen waters known as Racoczy and in the celebrated Sprudel of Carlsbad. The mineral content of these waters per litre is as follows:—

	Racoczy.	*Sprudel.*
	Grams.	Grams.
Potassium	0·1505	0·0840
Sodium	2·2977	1·7603
Calcium	0·5275	0·1286
Magnesium	0·2015	0·0475
Iron	0·0152	0·0015
Chlorine	3·9079	0·6280
SO	0·4706	1·7268

Both waters also contain the CO_3 ions in abundance, and the Racoczy has a considerable amount of free carbon dioxide. The important difference between these waters lies in their different content of Cl and SO_4 ions. While the Racoczy contains a high percentage of chlorine, the Sprudel only contains about one sixth as much. On the other hand, the Sprudel contains the SO_4 ions in considerable concentration, while the Kissengen water is poor in them. In consequence of these characteristics the Racoczy is readily absorbed and its constituents pass rapidly through the blood into the urine, the quantity of which may be considerably increased. The alkaline carbonates in the water also render the urine less acid in reaction. The Racoczy water thus exemplifies the type of alkaline water rich in chlorides. Other waters with similar properties are Vichy and the Hawthorn, Congress, and Vichy waters of Saratoga. These waters, however, contain little or no iron. Waters containing the chlorides in abundance and a moderate amount of alkaline carbonates are much in vogue for the treatment of gout, chronic rheumatism, the uric acid diathesis, gall-stones, obesity, and catarrhal derangements of the respiratory and digestive tracts. It is important for you to understand that they probably have no specific virtues, but act beneficially in part by encouraging the free use of water by persons who habitually drink too little, and in part by furnishing an abundance of basic alkali to tie and carry out organic acids that may be present in excess in the tissue cells and blood. A further advantage in many instances is the reduction in the excessive acidity of the

urine, which in many dyspeptics renders the bladder too irritable and in some instances favours the separation of uric acid in the urinary tract. But though these are actual and intelligible effects you should not lose sight of the fact that much of the benefit ascribed to these waters of which I am speaking comes from the more rigid habits of life with regard to diet and exercise, which usually form part of a course of treatment at the different spas. Without wishing to underrate the indefinable but nevertheless distinct utility of alkaline waters I ask you not to place the kind of reliance on such waters, which leads some practitioners to lose sight of the more important therapeutic indications connected with the revision of the life habits of their patients.

The other type of waters of which I shall speak is exemplified by the Carlsbad Sprudel, which, as already mentioned, contains the SO_4 ions in considerable concentration. Owing to the irritant action of the ions on the mucous membrane of the digestive tract the Sprudel is a powerful cathartic. The cathartic action of the SO_4 ions is observed in many other alkaline and saline purges, as for example in the Püllna water of Bohemia, the Friedrichshall of Germany, the Hunjadi János of Hungary, the Rubinat and Villacabras of Spain, the Epsom of England, and some of the Saratoga waters in New York State. The Rubinat water is perhaps less disagreeable than the others. All these are concentrated waters and owe their cathartic action in part to the fact that they are so strongly hyperisotonic as to abstract water from the blood. There are two effects of repeated purgation on which the therapeutic results of these various ' bitter waters ' chiefly depend. One is that persons who habitually eat freely are relieved by the saline cathartic from the absorption of an excessive amount of food material. The other consists in the removal of many products of excessive putrefaction in the intestine. The drawback to the use of such concentrated salts is the risk of setting up chronic catarrhal gastritis and enteritis, with the consequent impairment of the process of absorption. This diminished power of absorption often leads to serious impairment of nutrition. I therefore caution you in reference to the frequent use of strong saline cathartics: if you do not prescribe them with judgment they will do more harm than good. I have records of a number of patients in whom a chronic gastritis has appeared to be a consequence

of the habitual use of salts for laxative effects, and I have thus learned to prefer other cathartics. Some persons, however, use them with apparent benefit for years. The occasional use of laxative salts is ordinarily unobjectionable if the solution be employed in moderate concentration ; but even then it may exaggerate existing gastritis.

LITERATURE.

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Brasch, R. Ueber die chemische Konstitution und Wirkung der anorganischen Salzlosungen nach den Theorien der modernen Chemie. 'Zeitschrift fur diätetische und physikalische Therapie,' Bd. iii. 1900, s. 688. Die anorganische Salze im menschlichen Organismus. Wiesbaden, 1900.
Readable and suggestive, but highly speculative in places (*e.g.* the salts of the blood cells, pp. 63 and 64).
A valuable work, but one abounding in improbable hypotheses. For example, the writer holds that the HCl of the gastric juice is secreted as the result of physico-chemical processes without

implication of the epithelial cells. HCl is only secreted when NaCl is in the stomach. Now this NaCl is in part dissociated into the ions Na and Cl. Similarly in the blood the H_2O is in part dissociated into H and OH ions. The gastric wall is impervious to Cl ions but not to Na ions, which pass into the blood, while the H ions in the blood pass in the opposite direction to the stomach, where they unite with Cl ions to form HCl. It is to be noted in connection with this ingenious idea that the dissociation of H_2O into its ions is infinitesimally small. Further a most important objection to this idea is that stimulation of the vagi causes free secretion of HCl, even when the stomach contains no NaCl, or indeed no food material of any kind.

Students interested in the biological significance of the inorganic salts should read the important original papers of Jacques Loeb relating to this subject. Many of these papers are published in recent numbers of the ' American Journal of Physiology.'

LECTURE V

THE IRON OF THE FOOD AND ITS FATE IN THE BODY.—ALCOHOL.—THE ORGANIC ACIDS OF THE FOOD.—TEA AND COFFEE

Wide distribution of iron in food-stuffs—Organic and inorganic iron—Absorption of iron—Course after absorption—Income and outgo of iron—Excretion by the intestinal epithelium—Bunge's hypothesis of iron absorption—Objections—Hæmoglobin as a source of food-iron—Conversion of iron into hæmoglobin—Observations of Gaule—Alcohol—Extremes of opinion regarding its action—Food value of alcohol—Oxidation and decomposition within the organism—Caloric yield—Intake of oxygen and output of carbon dioxide under influence of alcohol—Alcohol as a saver of fats and carbohydrates; as a saver of proteid—Technical difficulties—Alcohol as a 'protoplasmic poison'—Influence of alcohol on the nervous system; on susceptibility to infection; on the heart and respiration—Effects of alcohol on digestion—Structural alterations induced by alcohol—Direct action of alcohol—Important effects of alcohol secondary to gastritis—Toxic action on the germ-plasm—Effects of habitual use of alcohol in small amount—Therapeutic uses of alcohol—Varieties of alcoholic drinks—The organic acids of the food: their oxidation in the organism—Tea and coffee: composition and physiological effects—Detrimental effects—Lack of food value.

In previous talks I have tried to bring to your notice some of the leading facts in reference to the chief types of food-stuffs. To-day I shall tell you something about several important materials that form a part of the food or drink, and which require some consideration by themselves.

Probably you are already aware that the food of man, like the food of all mammals, contains a small percentage of iron, an element absolutely essential to the maintenance of life, not merely in animals but also in plants. This iron is present in most kinds of animal and vegetable food, since the nuclei of all cells probably contain it in small amount. The quantity of iron in different articles of food varies considerably, though it is in all cases small. For instance, the

muscular substance of animals which we use as meat contains less iron than the livers from the same animals. Milk contains only a very low percentage of iron—a fact which has led some writers to condemn its exclusive use during infancy. The yolks of the fowls' eggs, so extensively used as food, contain a considerable percentage of iron, enough indeed to meet the demands of the growing chick. A certain amount of iron is present as hæmoglobin in the blood, which we consume in small amounts with the animal tissues served on our tables. Iron from this source has been considered to have no influence on nutrition, but the most recent observations bearing on this point indicate that this is an untenable view.

The cereals which we consume as bread, and in the form of porridge, contain iron in sufficient amount to constitute an important source of the metal. Wheat bran is said to be especially rich in its iron content. Spinach also contains more than the average quantity found in vegetable foods.

The iron of our food occurs in organic combination in union with proteid material. The iron which we prescribe for medicinal purposes is sometimes in the organic form, but more often it is in the inorganic state. Very likely you have a clear notion of the difference between organic and inorganic iron, but in case you have not, let me briefly explain this difference. Inorganic iron or iron in the form of ordinary salts undergoes electrolytic dissociation, and owing to this fact is capable of reacting with ammonium sulphide to form a black precipitate of ammonium sulphide, and with potassium ferrocyanide and potassium ferricyanide to make the well-known blue compounds of iron. On the other hand tests like these fail in the case of organic iron, and it has been suggested that this is owing to the iron being united directly to the carbon of the compound. Hæmoglobin and some allied substances are good examples of organic or 'masked' iron, as I should prefer to call it. The acetates, citrates, and other compounds of iron with organic acids resemble the chlorides, the sulphate, and other salts of inorganic acids. Their iron undergoes dissociation in solution, and is not organic iron in the special sense in which I am using the term, though united to organic acids. The same is true of albuminates of iron. I do not wish to give you the idea that we can make an absolute distinction between inorganic and organic iron, for there are com-

pounds whose behaviour is such that we cannot readily class them.

The compounds of iron have been so much used for medicinal purposes that considerable attention has been devoted to studying their absorption from the digestive tract. I cannot enter into a prolonged discussion of the various theories that have been advanced in this connection, but will undertake to tell you something of the present status of the question of iron absorption.

It has now been proved experimentally that iron undergoes absorption and follows the same course in the tissues, whether it be food-iron in organic form or whether it be ordinary iron in the form of salts. It is important for you to remember that this conclusion has been reached, because the view that inorganic iron fails to be absorbed has been stoutly advocated. In what form iron is absorbed we do not know positively, but such evidence as we have in relation to this point favours the view that almost all preparations of iron are at least partly converted into chlorides by the action of the gastric juice, to be absorbed as such, or after further conversion into albuminates. It is thought that the absorption of iron takes place chiefly from one part of the digestive tract, namely, the duodenum. The basis for this view is that if we kill animals which have been fed with preparations of iron and then examine the mucous membrane of the stomach by means of appropriate methods the epithelial cells of the duodenum are found to contain numerous granules of iron, whereas the epithelia of the stomach and the greater part of the small intestine do not show the presence of such granules. Some investigators, however, have observed indications of slight absorption from the stomach and jejunum as well as from the duodenum.

By means of methods similar to those that have been employed in studying the absorption of iron it has been possible to follow with some degree of accuracy the course which iron takes after absorption. It has been shown that soon after administering compounds of iron the granules just mentioned as appearing in the cells of the duodenum appear in the lymph nodes of the mesentery, are present in abundance in the spleen, and are found in lesser numbers in the liver and in the cortex of the kidney. If the tissues of an experimental animal be examined several days after giving iron, instead of more promptly, the distribution of the

granules is somewhat different. The chemical reactions indicating iron are less intense in the duodenum, spleen, and mesenteric nodes, whereas they are much stronger in the cells of the liver; and the epithelial cells of the large intestine and cæcum now indicate the presence of the metal. The meaning given to this distribution of the metal in the tissues is that after absorption from the duodenum it passes through the lymph channels to the blood, and is deposited first in the spleen, and that later it passes by way of the blood to the liver, where it is temporarily stored to be eventually removed by the blood and excreted by way of the epithelial cells of the colon and cæcum. One might perhaps anticipate that the iron deposited in the liver cells would be excreted by way of the bile, for it is true that a small quantity of iron is always present in this fluid. Experiment, however, indicates that iron given by mouth or injected into the blood does not increase the ordinary percentage in the bile.

A small quantity of iron suffices for the needs of the human body. It has been estimated that about $2\frac{1}{2}$ to $3\frac{1}{2}$ grams (40 to 55 grains) of iron exist in the structures of a healthy human adult, a quantity sufficient to make a small nail. The greater portion of this moderate possession is in the form of the hæmoglobin of the blood.

The chemical changes and the transfers in the location of the tissue iron are slowly effected, and involve only small quantities of the metal. It was once supposed that about 50 milligrams (1 grain) of iron are taken daily with the food, but modern investigations show that this estimate is much too high. An ordinary dietary contains not more than 5 to 10 milligrams ($\frac{1}{12}$ to $\frac{1}{6}$ grain), and this amount or even a smaller quantity suffices to keep the iron equilibrium undisturbed, that is to say, suffices to keep the income equivalent to the outgo. The outgo of iron occurs by two channels, the urine and the fæces. Of these two excretory paths the latter is far the more important, since it is possible to recover from the urine not more than 0·5 to 1·5 milligram of iron daily, or about one tenth the total amount of the food-iron. The rest of the food-iron leaves by the fæces.

One might readily be tempted to make inferences as to the absorption of iron from the relative quantities of the metal in the urine and fæces. Such inferences are liable,

however, to lead us into error, because it is a well-established fact that iron, like calcium, is excreted by way of the intestinal epithelium, and this, of course, makes it possible that some of the iron in the stools may have been absorbed and excreted again. The failure to recognise this fact is responsible for some serious errors in reference to the absorption of iron, and is one of the things that led Bunge astray in formulating this well-known theory. This ingenious theory of iron absorption has been so widely discussed, is so plausible, and has so greatly stimulated investigation, that I cannot properly omit a short reference to it.

Barely stated the hypothesis of Bunge is that ordinarily the body continually loses a small amount of iron by the excreta, and that this small but steady loss is compensated by the iron contained in the food. This iron is in the organic form, that is to say, combined, as I have already explained to you, in such a manner that it does not readily react with sulphur compounds to form sulphides. In health the iron of the food replaces that lost by excretion, but in states of anæmia, such as chlorosis, large amounts of sulphides are supposed to be present, and these lead to a decomposition of the organic iron, which allows this iron to combine with the sulphides to form ferric sulphide. But ferric sulphide is insoluble, and hence cannot be absorbed. Thus the organism grows poorer and poorer in iron.

If under these circumstances inorganic preparations of iron be given—ferric chloride or sulphate for instance—they form sulphides, and thus save the organic food iron from decomposition. Therefore the food iron is absorbed and utilised as in health, and the anæmia improves.

You perceive that according to this hypothesis the inorganic iron does not act after being absorbed, but merely by replacing the food-iron that is attacked, and thus putting a check on this harmful diversion of the necessary metal. Bunge and others even went so far as to deny that inorganic iron is ever absorbed by normal epithelial cells, and stated that even if absorption occurred to a slight extent through injured epithelia the inorganic iron would still be useless, because the animal body is incapable of performing the elaborate synthesis into hæmoglobin.

One of the most important contentions in favour of the Bunge hypothesis was that inorganic iron administered by the mouth is not followed by an increase of the iron in the

urine. The assumption was made that if any of this iron were absorbed it would surely appear in the urine in the course of time. But this assumption has proved to be wholly erroneous. It is now well settled that when a salt of iron, such as the double tartrate, is injected directly into the circulation the iron soon disappears from the blood, to be stored up in the liver and spleen. Only a very small percentage of the iron reappears in the urine, even where considerable quantities are thus directly introduced into the blood. It is in fact clear that considerable iron may be introduced into the organism, either by direct injection or by absorption from the intestine, without any significant increase in the iron content of the urine. Thus you see that Bunge was led into serious error by this inference that the iron of the urine is a reliable index to the absorption that occurs from the intestine. He overlooked the considerable accumulation of iron that may occur in the liver, spleen, and elsewhere.

There are other serious objections to the hypothesis of Bunge which I ought at least to mention, notwithstanding the fact that this investigator has modified his original views in several respects. In the first place it is clear that if the common inorganic preparations of iron acted only indirectly through the power to bind the sulphur in the sulphide of the intestinal contents, other metallic salts would act quite as efficiently in the cure of anæmias. But this they fail to do. Then, again, it has been shown that iron injected hypodermically instead of by mouth is capable of exerting the well-known effect in bringing about an increase in the hæmoglobin of the blood in chlorosis. Moreover, iron loses none of this therapeutic influence when we give it as a sulphide. Lastly there is the crowning fact already mentioned that experiment proves the ordinary inorganic salts of iron to undergo absorption from the gastro-enteric tract.

I referred a short time ago to the view that hæmoglobin is useless as a source of food-iron. This view was based on the fact that hæmoglobin, whether contained in the blood or in the crystalline form, is readily converted into hæmatin, a body which is believed to be absorbed from the intestine only to a very limited extent. The experiments of Abderhalden upon the absorption of iron in rats show that the administration of hæmoglobin or of hæmatin with the food is regularly followed by an increase in the hæmoglobin of the blood, which can only

be explained on the supposition that the iron of these substances is to a considerable extent absorbed. We are therefore not justified in assuming that the iron of hæmoglobin and hæmatin has no nutritive value. It must, however, be owned that the status of these bodies as iron-holding and blood-forming ingredients of the food cannot be regarded as settled for the human subject.

The experiments to which I have just referred showed one noteworthy difference between the action of inorganic iron and iron combined in hæmoglobin; while the former appeared to stimulate the growth of the organism, the latter failed to do so.

The formation of hæmatin from hæmoglobin may occur either in the stomach or in the intestine. Even moderate quantities of hæmatin impart a dark-brown colour to the stools. This is the explanation of the tar-coloured fæces observed where there has been a hæmorrhage into the digestive tract. The fæces may be considerably darkened even in consequence of a diet rich in blood-holding meat.

At the present time we know almost nothing of the chemical changes undergone by iron after its absorption in conditions of health; it is therefore not surprising that we should be equally ignorant of the nature of the transformations through which iron passes under pathological states. That some portion of the food-iron becomes converted into hæmoglobin is almost self-evident, but the processes attending this conversion are still most obscure.

The observations of Gaule show that the iron-free lymph in the thoracic duct in rabbits can be altered to an iron-holding lymph by the administration of a very weak solution of iron chloride by the stomach. The iron in the lymph of the thoracic duct is not, however, ferric chloride, nor indeed inorganic iron, but exists as an organic combination, probably as an albuminate. That the organism is capable of effecting the synthesis of this iron into hæmoglobin is indicated by a prompt increase in the hæmoglobin content of the blood, which is followed after a short period by an increase in the number of red blood cells. Apparently the spleen, the bone marrow, and the liver are especially concerned with the synthesis of hæmoglobin, but we are quite in the dark as to the character of the synthetic steps.

We know nothing of the chemical state of the iron in the cells of the liver and spleen and in the cells generally.

There is good reason to believe, as I mentioned to you in speaking of the chemical defences of the organism, that iron exists in the tissues in at least two different stages of oxidation, a higher and a lower, and that the all-important capacity of iron salts to facilitate the transfer of oxygen to living protoplasm is closely connected with alternate oxidations and reductions in these iron compounds. Where there is an excessive amount of iron in the organism, as after the administration of large doses, the iron stored in the cells may exist either in the same form or forms as under normal conditions or in some unusual chemical combination. In what form the iron of the urine exists is entirely unknown. In pathological conditions attended by a rapid and considerable destruction of blood the hæmoglobin undergoes changes which lead to a considerable deposit of its iron in the various tissues, especially the cells of the liver and spleen. This iron is present in the form of a granular pigment, and is recognisable by means of appropriate micro-chemical reactions, but the precise nature of the compound is not known. This iron-containing pigment is called 'hæmosiderin.' In the peculiar condition of disease known as general hæmachromatosis this iron-holding pigment is very widely distributed in the body, and is present in enormous amounts. Doubtless the excessive destruction of blood is essential to effect such depositions of iron, but it is clear that other factors of unknown character must also be in operation, since only a much more moderate deposition is occasioned by the most active blood destruction observed in states like pernicious anæmia or in poisoning by blood-destroying drugs like toluylendiamin.

But it is not my desire to discuss the relations of iron to pathological conditions. It is my intention to speak of this subject in connection with what I have to tell you about the chemical pathology of the blood. Nor is it my wish to consider now the action and uses of iron as a therapeutic agent. I have aimed particularly to acquaint you with some of the facts relative to the food-iron. The points which I wish you especially to bear in mind are the following :—

1. Iron is essential to the maintenance of animal life.
2. A mixed diet contains the necessary amount of iron.
3. The food-iron is masked or organic iron.
4. Both organic and inorganic iron undergoes absorption chiefly through the duodenum.

5. The iron absorbed is deposited largely in the lymph nodes, the spleen, and the liver.

6. Iron is excreted both by the urine and fæces, but chiefly by way of the latter.

7. The quantity of iron excreted by the urine and fæces gives us no reliable indications of the quantity of iron that has been absorbed, because some of the metal that has been absorbed is re-excreted by way of the colon.

8. Both the food-iron and the inorganic iron used in therapeutics are convertible into hæmoglobin by the organism.

Iron is probably not the only heavy metal that enters into the composition of the food, for copper and manganese are found in small amounts in the human tissues or fluids, and are doubtless introduced with the food. But these metals, unlike iron, do not form an integral part of the proteid molecule, and are not essential to life.

Another element which probably enters into the food in very small amounts is iodine. Recent studies of the secretion of the thyroid gland show that iodine is one of the constituents of this secretion, and there is good reason for believing that the metal plays an important *rôle* in connection with metabolic processes. I shall, however, reserve this topic until we take up the study of the thyroid secretion.

The rest of the hour I shall devote to the consideration of a subject that is of the highest interest to you, both as students of pathology and as students of social science. You will doubtless surmise that I refer to alcohol. Few material things have received more praise or greater condemnation. The *bon vivant* praises without stint the favourite vintage in his wine cellar, and the world contains many people who are convinced that a drink of whisky two or three times a day or a bottle of wine at meals is essential to the maintenance of sound health. On the other hand, the teetotalers tell us that alcohol is a poison which should not be drunk in any form, and some of the more enterprising and partisan of these people have actually succeeded in bringing about the use of text-books of physiology in the public schools in which the teachings of science are distorted to meet their own extreme and unscientific views.

It is perhaps not surprising that the views of laymen

should be thus divided on a subject which, like the use of alcohol, involves the unbiassed recognition of many physiological conditions. But we find, unfortunately enough, that even among intelligent practitioners of medicine and among physiologists widely divergent views are held in reference to both the action of alcohol and the advisability of using it as an ingredient of our drink. The extremists among the learned, like the extremists of the laity, are divided into two opposite camps, one of which insists that alcohol is a food, while the other is equally positive that alcohol is a poison and nothing else. It is so important that you should have accurate and unbiassed ideas on this subject that I shall try to lay before you the results which have been reached by unprejudiced workers on this special problem, although it is proper to say at the outset that there are many points connected with the alcohol question which have not yet received sufficient study to justify positive conclusions. Moreover it will not be posssible for me to enter into full details as to the experimental data on which are based some of the statements which I shall make.

It seems to me best that we should first discuss alcohol as a food, then its action upon the nervous system and the digestive organs, and next its influence in the production of pathological conditions.

That the value of alcohol as a food should have been widely debated is not in the least surprising when we consider first the extensive consumption of alcoholic drinks; and secondly the technical difficulties incidental to inquiries relating to food values. It is important for us to know whether the alcoholic drinks which we use so freely in health possess a food value, and if so how great is this value. It is also important for us as physicians to know whether the alcohol which we give in the course of many acute and chronic diseases is merely a temporary stimulant to the nervous system, or whether it has also a distinct nutritive value.

In order to prove that any material possesses actual nutritive properties there are two questions which must be answered in the affirmative. One is, Do the cells of the body decompose and oxidise the substance under consideration with a liberation of the potential energy belonging to the compound? You will readily understand the importance of this question when you reflect that many substances pass

through the organism without being decomposed, and hence without liberating energy.

Having shown that the body under consideration is actually capable of being decomposed and oxidised in the organism with a liberation of energy, we have to put the second question: Is the body under trial decomposed in such a way and under such conditions as to enable the organism to utilise the energy that is liberated? You can readily see that if decomposition took place completely or partially in the intestinal tract the energy yielded would be entirely or partially lost to the organism. Similarly it is conceivable that the decomposition might occur after absorption from the intestine without being so utilised as to replace other elements of the food or constituents of the tissues. But it is evident that the real food value of any compound depends on its ability to replace other food like the fats and carbohydrates, and like them spare the proteids of the tissues from combustion.

Not very long ago opinions were divided as to whether alcohol is largely decomposed and oxidised in the body, many writers maintaining that it passes through the body to a considerable extent unaltered. This contention has now been definitely abandoned, for it has been proved that the proportion of alcohol which leaves the body is extremely small. The small percentage of unburned alcohol in the exhalation and urine varies somewhat according to the conditions of the experiment, but probably seldom exceeds 2 or 3 per cent. of the amount introduced, and is often not more than 1 per cent. even where the dose equals 100 grams of alcohol daily. By far the greater portion of the alcohol is oxidised into water and carbon dioxide.

It is easy to show that when a moderate quantity of alcohol is burned in the body to water and carbon dioxide there is a simultaneous liberation of a considerable amount of chemical energy. This is expressed by saying that alcohol has a high caloric value. You will remember that I told you one gram of proteid and one gram of carbohydrate material each yield 4·1 large calories, whereas one gram of fat yields 9·3 large calories. Now one gram of alcohol on being burned either outside or inside the animal body yields seven large calories or considerably more than one gram of proteid or carbohydrate, though not so much as one gram of fat. Therefore 100 grams

of alcohol (a little more than three ounces) yields in the organism 700 calories if wholly burned. Estimating the total caloric needs of an adult of average weight at 2,800 calories in twenty-four hours, we see that 100 grams of alcohol would supply a quarter of the total requirement for a day.

We come now to the second question : Is alcohol utilised in such a manner in the human body as to save the other elements of the food or the tissues of the body from being burned, or are the food-stuffs and the tissues of the body burned to meet the caloric requirements, just as though no alcohol were given ?

The answer to this question can only be obtained by studying the end-products of metabolism under the influence of alcohol and without this influence. You know from your studies of physiology that the intake of oxygen by the lungs and the output of carbon dioxide give us an index of the intensity of metabolism. If now we know the oxygen intake and the outgo of carbon dioxide in an individual on a known diet, we can find out how the metabolic processes are affected by the use of alcohol when a given quantity of alcohol is added to the known diet. If the combustion of the tissues and ordinary food goes on just as actively when the alcohol is given as when it is not given, the metabolism of the body must be increased in proportion to the alcohol administered and burned. But if, on the contrary, the alcohol administered actually replaces some portion of the food or of the tissues, so that they are saved from combustion, then the end-products of combustion either will not be increased at all or will be increased much less than in the case which I have just mentioned. The technical difficulties which surround an investigation of this sort are so great that there have been many conflicting results—results from which it is impossible to draw any satisfactory conclusions. The experiments of Zunz and Geppert, carried out in 1887 with painstaking care, appear to have settled conclusively the question to which I have just referred. These observers found that the consumption of alcohol neither materially increased the intake of oxygen by the lungs nor altered the outgo of carbon dioxide. Hence we may say that alcohol does not simply undergo combustion in the body without affecting metabolism, because if this were the case the intake of oxygen and the outgo of carbon dioxide would be increased. There is

no doubt that when alcohol is decomposed and oxidised in the body other substances belonging either to the food or to the tissues are saved from combustion. This is only another way of stating that alcohol has the character of a nutrient material, a proposition which you may look upon as having been established. But the proposition that alcohol has the character of a nutrient material does not precisely fix the position of alcohol as a food. The question which you will naturally ask is, What nutrient materials is alcohol capable of replacing? Does alcohol save from combustion the carbohydrates, fats, and proteids, or only carbohydrates and fats?

As you are already aware, we may regard the stored fat of the body as a nearly lifeless mass of material on which the organism may in times of need draw extensively for caloric purposes, or, as we may say, for the purpose of furnishing heat to the machine, if we employ the somewhat abused analogy between the bodily apparatus and the steam-engine. On the other hand, the proteid of the body is the material of which the living cells are built—material which not only yields heat to the machine, but which forms an integral part of the engine. If it could be shown that alcohol saves fat from combustion, the fact would entitle alcohol to a position as a food material; but if it could be shown that alcohol spares proteid from combustion, as does fat, its position as a food would be a somewhat higher one, and would entitle it to comparison with fatty and carbohydrate food. This difference between alcohol as a saver of fat and alcohol as a saver of proteid is of comparatively little importance in states of good nutrition where there is vigorous health, and the tendency of the body is to gain proteid rather than to lose it. In pathological conditions attended by wasting, with continual loss in proteid, this difference may assume greater importance, though hardly so great importance as is sometimes attributed to it.

How are we to decide whether alcohol merely saves fat or whether it is also capable of saving proteid? Such a decision can only be reached by means of observation involving the most careful comparison between the amount of nitrogen taken with the food and the amount of nitrogen lost by the urine and the fæces. You know that if we keep a normal person on a general and sufficient diet containing the same amounts of the same food constituents from day to

day, with a fixed and known amount of nitrogen, it is possible to bring the subject of the experiment into a state of nitrogenous equilibrium. When in this state of nitrogenous equilibrium he excretes by the urine and fæces a quantity of nitrogen almost exactly equal to the amount of nitrogen which he takes in. The body of a subject in this state neither loses nor gains nitrogen.

Suppose now that we vary the conditions of the experiment somewhat. Suppose that we add to the regular dietary of the subject a considerable quantity of fat or of carbohydrate food. The subject no longer remains in nitrogenous equilibrium. The quantity of nitrogen excreted grows less than under former conditions, although there is no diminution in the nitrogen income. The body holds back proteid material which it adds to its cells. In other words, the fat or the carbohydrate food, whichever may have been used, has acted as a saver of proteid.

Let us now suppose that the subject of the experiment just mentioned is again placed in nitrogenous equilibrium, and that instead of increasing the diet by means of fats or carbohydrates we add alcohol to the diet. If the alcohol, like fats and carbohydrates, saves proteid, there will be a retention of proteid in the organism, as shown by a somewhat diminished excretion of nitrogen. The ability of alcohol to save proteid can be tested in another way. Having brought the subject into nitrogenous equilibrium a certain amount of fat or carbohydrate is replaced by an isodynamic amount of alcohol; that is, an amount of alcohol having a caloric value equal to that of the food which the alcohol is designed to replace. If the alcohol completely replaced the fats or carbohydrates, the subject would lose no nitrogen, but would remain in nitrogenous equilibrium.

Now, in order to obtain really conclusive results by means of such experiments as these, it is essential that the observations should be carried on with a high degree of intelligence and with the most conscientious regard to the details of technique. Most of the experiments that have been undertaken are open to criticism of one sort or another, and the number of observations that are without technical error is very small—too small, in fact, to enable one to say that the position of alcohol as a saver of proteid has been finally settled. My interpretation of the modern experiments

relative to this question leads me to the following conclusions: First, alcohol is capable of replacing in a large measure the fats and carbohydrates of the food. If you give a normal adult 100 grams of alcohol in place of an isodynamic amount of fat, the fat is very largely, if not wholly, replaced by the alcohol. The same is true of the replacement of carbohydrates. Experiments show that animals receiving alcohol lay up more fat than animals receiving the same food without the alcohol, and this result accords well with the commonplace observation that many people who habitually use alcoholic drinks with freedom grow fat.

In the second place it has not yet been demonstrated conclusively that alcohol is capable of completely replacing the fats and carbohydrates even where only a small portion of the dietary is substituted by alcohol. We have not at present the data that enable us to say that alcohol saves proteid from waste to the same extent that fat saves proteid. On the other hand, we are not justified in saying positively that alcohol never saves proteid waste, because there are isolated experiments which render it not unlikely that alcohol is under some conditions a moderate saver of proteid. It seems clear, however, that the most enthusiastic defenders of alcohol as a food are not at present entitled to make the general claim that alcohol spares proteid. If we consider the most reliable experiments that have been made, we find that the majority have shown alcohol to be incapable of sparing proteid from combustion.

I would discuss more fully this question of the ability of alcohol to save proteid if we had ample time at our disposal. The extensive literature relating to the subject indicates how large a share of attention has been given to determining whether alcohol does or does not save proteid. But it seems to me that, important as the subject is from a physiological standpoint, its practical significance has been considerably exaggerated. Even those persons who are most friendly to the use of alcohol as a food do not propose to replace wholly or even largely the carbohydrates and the fats by means of alcohol. If we admit, for the sake of argument, that the substitution of a hundred grams of alcohol for an isodynamic amount of fat or sugar is regularly followed by a small loss of proteid in a person previously in nitrogenous equilibrium, this cannot in itself be regarded as an objection to the use of the alcohol in the

absence of other objections. The continued loss of nitrogen might ultimately be detrimental, but the occurrence of a detrimental loss can readily be prevented by increasing the amount of proteid food. I am strongly of the opinion that the practical objections to the use of alcohol have little to do with the question whether alcohol can or cannot save proteid. These objections are based on the injurious effects of alcohol on the cells of the digestive tract and on the cells of the nervous system.

A question of considerable interest which arises in connection with investigations of alcohol as a saver of proteid is whether alcohol has the action of a 'protoplasmic poison.' In certain experiments of Miura, Stammerich, Keller, and others, there was observed a small loss of nitrogen in a period following the administration of alcohol, and this small loss has been interpreted to mean that alcohol directly injures the cells of the body, and is therefore to be classed with chloroform and some other destructive agents as 'protoplasmic poisons.'

I consider it impossible to decide from the evidence now available whether we are justified in speaking of alcohol as a protoplasmic poison on the ground of its increasing nitrogenous waste. We know sufficiently well the injurious action of alcohol on unicellular organisms and on the cells of the human body, but it has to be remembered that the grade of concentration has much to do with these effects. Considerable quantities of alcohol can certainly be taken by human beings in a 1 per cent. solution without structurally injuring either the epithelial cells of the digestive tract and its glands or the cells of the central nervous system. We know further that many persons take considerable alcohol during long periods of time without apparently losing nitrogen.

On the whole it seems probable that the injury which alcohol inflicts on cells depends very largely on the quantity and concentration of the alcoholic drink. I do not consider it proven that a moderate use of alcohol necessarily causes a loss of nitrogen from injury to protoplasm. Neither is it clear that alcohol causes an increased output of nitrogen even in cases where it certainly does injury to the epithelial cells of the stomach, to the cells of the liver, &c. Further studies are necessary to determine under what conditions, if any, alcohol is a 'protoplasmic poison' in the special sense.

It is thus an undeniable fact that alcohol possesses a

distinct food value based on its ability to replace fats and carbohydrates, and, as I shall explain to you later, this food value may sometimes be advantageously utilised in the treatment of disease. But I beg you not to draw the inference that the food value of alcohol justifies its frequent or general use as a drink. The truth is that while alcohol must technically be regarded as a food there are physiological and pathological obstacles to its use which are of the first importance. These obstacles consist of a series of well-defined effects which alcohol exerts upon the different cells of the organism. I shall show you when we come to the pathological action of alcohol that these effects go a long way towards neutralising any practical value which alcohol may possess as a food-stuff for habitual use.

The action of alcohol on the nervous system in moderate doses varies somewhat according to individual susceptibility. In most persons there is at first a sense of exhilaration and of well-being, which is usually followed by a stage of excitement. In this stage of excitement the subject is characteristically loquacious and exhibits various evidences of a loss of self-control which vary a good deal according to the individual disposition. If the dose of alcohol be sufficiently large the speech becomes difficult, and the gait has the staggering character which makes the nature of the intoxication apparent even to the casual looker-on.

Still larger quantities of alcohol give rise to deep sleep followed by unconsciousness, with loss of the knee-jerks and certain other reflexes. The unconsciousness induced by alcohol resembles that of chloroform anæsthesia, but is of longer duration, and frequently terminates fatally from failure of respiration.

There are two entirely distinct views as to the action of alcohol on the nervous system. According to one of these alcohol first stimulates and later depresses the nerve-cells. According to the other, alcohol really never stimulates the nerve-cells, but depresses them from the very beginning. According to this view the symptoms of excitement which we notice after a considerable quantity of alcohol has been taken are due, not to an actual stimulation of the motor neurons of the nervous system, but to a depression of those higher centres which normally exert a restraining influence on the motor structures of the brain and spinal cord. It is difficult to say which of these views is correct, but the latter

appears to have much in its favour, especially the fact that even small doses of alcohol lessen the activity of the highest functions of the brain and benumb especially those functions which have been slowly acquired through experience and education. The brilliancy of speech sometimes noted in persons under the influence of alcohol can probably be explained on the ground that the speaker loses his habitual reserve and the consciousness of his own limitations.

The indications of the depressing effect of alcohol are very numerous. It is well recognised now that troops do more sustained work without alcohol than with its use. It is true that the most carefully conducted experiments show that moderate doses of alcohol at first increase the working capacity of the muscles, but this primary increase is followed by a well-marked depression in working power. Thus the effect of alcohol is to render the output of work uneven, which is an undesirable thing where we wish sustained effort. The initial increase in muscular power is associated with an increased excitability of the peripheral motor nervous mechanism, but it is unknown whether there is a similar increased excitability of the central nervous system.

The depressing effect of alcohol has also been noted in forms of labour involving a high grade of intelligence and accuracy in the use of the muscles. Thus type setters were found to make fewer errors and to do more work when they abstained from alcohol.

It is exceedingly difficult to measure with accuracy the effect of alcohol on intellectual work, but Kraepelin, a very careful observer, found that the receptive and intellectual powers were weakened even by small doses of alcohol, while the motor activities were somewhat increased by small quantities and depressed by larger amounts. Kraepelin reaches the conclusion that even small amounts of alcohol do not actually increase the capacity for either intellectual or muscular exertion, and the most intelligently conducted investigations give support to this view.

It is therefore evident that you are not justified in recommending the use of alcohol as a beverage with the expectation of increasing the capacity either for mental or for mechanical work.

Among the depressing effects of alcohol we may probably place its action upon the sense of fatigue. The feeling of

fatigue which develops after arduous exercise is conservative in its effect of restraining people from excessive and perhaps injurious effort. Alcohol unquestionably benumbs the sense of fatigue, and by removing this conservative regulatory influence renders persons more liable to extravagant and harmful expenditures of energy.

One of the most important effects of alcohol has to do with the susceptibility to infection. It has now been clearly shown that the susceptibility of animals to experimental infections is distinctly and often greatly increased through treatment with alcohol. This is true both of intoxication with a few large doses and of the long-continued treatment with numerous small doses. There can be little doubt that the susceptibilty of the human animal to various infectious diseases is increased by the habitual immoderate use of alcohol; but whether this is true also of the habitual use of alcoholic drinks in very small amounts must be regarded as uncertain. The extreme opponents to the therapeutic use of alcohol are disposed to argue that alcohol is objectionable in fevers because it tends to increase the susceptibility to the infectious agents on which fever commonly depends. I question, however, whether this contention has any force, since there is no evidence that alcohol in therapeutic doses increases the danger of an infection already established. I would not advise you to refrain, on the ground of this contention, from the moderate use of alcohol in fever, where you desire to utilise its property of protecting the body against an excessive loss of fat, or where you wish its stimulating effect upon the secretion of gastric juice.

The effects of alcohol on the respiration and circulation are but imperfectly understood, though they have been much studied. When a considerable dose of alcohol has been taken there is usually a period in which the respirations and the cardiac pulsations are increased in number. As these accelerations are observed during the stage of excitement in which there is increased muscular activity, it is by no means always clear whether the increase in pulse and respiration is due to a direct action on the medullary centres, or whether it is merely the ordinary accompaniment of increased muscular exertion and the mental excitement that attends the use of alcohol. Although numerous experiments have been made to determine these points, we are still unable to say

positively that alcohol regularly increases the excitability of the respiratory and cardiac centres. On the other hand, there is no satisfactory evidence of an early depressive action on these centres in the case of man.

Individuals differ much in respect to these apparently exciting or depressing effects of alcohol. Some of the advocates of alcohol as a cardiac tonic claim that while the drug may not always increase the rapidity of the heart, it may increase its force. On this point it is difficult to pass judgment. My experience in the observation of the effects of small doses of alcohol on the heart in normal persons makes me think that such doses usually increase temporarily the work done by the heart. I have many times observed an increase in the frequency of the pulse following a small dose of alcohol, even when there was no increase in general muscular activity. I have also observed an increase in the force of the heart's action as measured by the effect on the heart-sounds. For these reasons I favour a moderate use of alcohol as a cardiac stimulant in some conditions of disease such as pneumonia. It is important not to overdo the matter of stimulation with alcohol, as is so often done in fevers.

The fact that experiments on dogs have shown the rapid intravenous injection of considerable doses of alcohol to be followed from the first by weakening of the efficiency of the heart should not prejudice us against its moderate use in febrile and other conditions, where mild cardiac stimulation is desired.

There is one other effect of alcohol on the nervous system to which I must refer. This is the dilatation of the blood-vessels of the skin. In consequence of this widening of the calibre of the small vessels the skin is flushed and the subject has an agreeable sensation of warmth, which, however, lasts only a short time. Another consequence of the vascular dilatation is a slight fall in the temperature of the blood of the internal organs, a fall seldom amounting to more than 0°·5 or 1° C. unless the dose be large enough to bring on a state of intoxication. If the subject use his muscles freely, this slight depression of temperature does not occur. The general blood pressure is not lessened by small amounts of alcohol.

We do not know the cause of the widening of the capillaries of the skin—whether it be of central or peripheral

origin, or whether it depends on stimulation of the vaso-motor centres or on paralysis of the vaso-contractors.

I wish now to tell you something of the effects of alcohol upon digestion.

When alcohol is taken into a healthy human stomach, even in dilute solution, it probably acts as a stimulant to the activity of the epithelia and leads to a more active circulation in the capillaries of the stomach wall. I speak of these effects as being probable because they have not been actually demonstrated in the case of the human stomach. All we can say is that experiments on animals show that there is a flushing of the mucous membrane with a more rapid secretion of gastric juice after the ingestion of alcohol, and that the more abundant secretion shows an increase both in acidity and in solid contents. It is true that experiments have been made on the human subject, but these show such contradictory results as regards the influence of alcohol on gastric digestion that we cannot safely draw any general inferences from them. Besides these observations on lower animals and on man there have been some test-tube studies of alcohol on the digestive ferments. The presence of very small quantities of alcohol either has no perceptible effect on the action of the gastric ferments *in vitro* or slightly increases their peptonising action. When the percentage of alcohol is increased to between 5 and 10 per cent., both the gastric and pancreatic ferments are much retarded in their action, the pancreatic secretion being prejudicially affected by smaller percentages than the gastric juice. The experimental evidence thus being so meagre, it is necessary for us to rely largely on the results of clinical experience in trying to form an opinion of the influence of dilute solution of alcohol on normal human digestion. The clinical evidence on this point seems to me to harmonise with the few experimental results to which I have just referred ; that is to say, they indicate that persons with normal digestion and sound health can take alcohol in the slight concentration in which it occurs in kumyss, matzoon, and weak beer without appreciable effects on the rapidity of digestion and the efficacy of the peptic ferment, or with a slight increase in the rapidity of digestion. The element of quantity is, however, of equal importance with that of percentage, and it seems probable that considerable amounts of alcohol, even in a dilution not exceeding 3 or

4 per cent., usually exert a retarding effect on digestion, especially where the use of weak alcoholic beverages is long continued. But there is certainly great variation among individuals with reference to the action of weak alcoholic drinks, and it is hardly possible without special investigation to form an opinion as to whether alcohol retards digestion in particular instances.

In cases where stronger alcoholic drinks are used habitually we see great differences in the results to the stomach according to difference in the individual tolerance, the concentration and quantity of the drinks used, and the duration of the practice. Some persons regularly drink at their meals wines containing as much as 8 or 10 or 12 per cent. of alcohol during many years without any clinical evidences of an impaired gastric or intestinal digestion. Probably gastric digestion is actually somewhat slowed in these cases, and there may doubtless be a distinct impairment both in gastric and intestinal digestion which during many years gives rise to no definite symptoms. Do not therefore assume because a person regularly takes a pint or two of claret or a similar wine during many years without apparent disorders of digestion that the alcohol cannot possibly be doing harm. It seems to me likely that in many of these cases of apparently harmless and moderate drinking of wine the way is being paved for a chronic gastritis which often seems of mysterious origin to both the patient and his physician. Another class of moderate wine-drinkers soon find that their daily allowance of wine is doing them harm, and sooner or later abandon the habit. Usually it is the signs of gastritis which lead them to give up the drinking of wine. You may perhaps ask if it is clear that the gastritic symptoms are really due to the alcohol and not to the presence of other substances present in the wine, such as organic acids, higher alcohol, &c. What evidence we have on this point indicates that it is to the alcohol chiefly that the gastritic symptoms are due ; but it cannot be denied that other constituents of wines and liquors are capable of interfering somewhat with digestion.

When we come to consider the effects of the habitual use of considerable doses of alcohol in the form of whisky, brandy, gin, &c., we find that there are very few persons who do not sooner or later exhibit definite evidences of pathological consequences referable to alcohol. Persons who

frequently drink to the point of exhibiting the mental evidences of intoxication probably suffer more serious consequences than those who never indulge to the point of intoxication; but since the susceptibility to these mental effects varies enormously in different individuals we cannot use the ordinary signs of intoxication as a wholly reliable measure of the effects of alcohol on the organism at large. It is well recognised that many persons who take large amounts of whisky without ever becoming drunk suffer more harm than persons who are more susceptible to the mental effects and therefore consume less alcohol, although they become frankly intoxicated from time to time.

The structural changes that are set up by alcohol in excessive drinkers are chiefly connected with the digestive tract, including its hepatic appendage, and with the central nervous system. The effects of alcohol on the structure of the digestive apparatus are of the first importance, although I can here only refer to them without undertaking their description. Since alcohol acts as a powerful local irritant, it is not singular that its first effects are exerted largely upon the mucous membrane of the stomach. The character of the gastritis which is thus set up differs somewhat according to the quantity and concentration of the alcohol and the duration of the excessive indulgences. The gastritis may have the character of an acute gastritis with much desquamation of epithelium, intense congestion, and perhaps some superficial ulceration, or it may have the features of a chronic process with atrophy of the mucous membrane and irregular patches of moderate congestion. Some experiments made several years ago convinced me of the readiness with which either acute or chronic gastritis can be induced in pigs by means of not very large doses of 30 or 40 per cent. alcohol. I observed that the congestion and the damage to the epithelium were by no means evenly distributed, but occurred in irregular patches near the pyloric end of the greater curvature.

The alcohol which passes into the stomach is readily absorbed in part from the stomach itself, in part from the upper part of the intestine. Perhaps a small proportion of it is decomposed and oxidised in the walls of these viscera, but it is certain that the greater part of the alcohol passes unchanged by the portal vein to the liver, even where the quantity taken is what would ordinarily be called moderate. As I shall explain to you on another occasion, the cells of the

liver are capable of carrying on the most intense oxidative activities. In virtue of these the alcohol which comes to the liver is rapidly oxidised to water and carbon dioxide, and it is probably only in the case of great excesses in drinking that much alcohol passes unaltered from the capillaries of the liver into the general circulation. But while the liver thus acts as a screen to the cells of the nervous system and other kinds of cells it is especially liable to suffer damage itself. The nature of the first injury inflicted on the liver cells by the unchanged alcohol is not fully understood, but it is certain that through its direct action alcohol is capable of inducing changes in the structure of the cell protoplasm which are connected with a decrease in the capacity of these cells to effect oxidative changes, not merely in alcohol, but in the ordinary nutritive substances which are normally burned in the liver. Thus it comes about that the liver no longer oxidises with normal intensity the fat which is brought to it, and hence the unburned fat accumulates in the hepatic cells. The reason why it is fat rather than carbohydrate material or proteid which thus accumulates is sufficiently simple. As I have explained to you in an earlier talk, fat is less readily burned than carbohydrates or proteids, and being constantly supplied to the liver by the blood it accumulates under conditions of diminished oxidative activity still sufficient to consume proteid and carbohydrate material. I look upon alcohol as one of the most important causes of fatty liver. The process of fatty infiltration is not, however, always confined to the liver, for if enough alcohol escapes burning in the liver the cells of the kidney may become injured similarly to the hepatic cells, though usually in much less degree.

Alcohol is very generally regarded as inducing connective tissue overgrowth in the liver, kidneys, and elsewhere. Thus many writers regard alcoholic excess as the preponderant cause of a certain type of hepatic cirrhosis, and the small granular kidney is supposed by some to be frequently induced by alcoholic excess. In the case of the kidney I have reached the conclusion, from a statistical study of the clinical histories and autopsy findings of many hundreds of patients, that there is little or no ground for the view that alcohol is a cause of small granular kidney. There appears to be no doubt that the excessive use of alcohol, especially in the form of strong drinks like whisky and gin, is one of the important causes of cirrhosis of the liver.

I consider it very important for you to recognise that the deleterious action of alcohol on the liver is by no means confined to the influence of alcohol as such. There is little doubt that alcohol, acting directly on the liver cells, is capable of inducing fatty infiltration of the cells, and it is probable that connective-tissue alteration arises in the same way. There is, however, a wholly different influence which commonly acts in connection with the alcohol as such. I mean the effects which are secondary to the gastritis which is so common and so prominent a result of alcoholic excesses. In consequence of chronic gastritis various disorders of gastric secretion and of motility arise in alcoholic patients, and these disorders lead to important fermentative and putrefactive alterations in the food. Owing to these pathological changes in the food the liver receives products of excessive putrefaction and fermentation which are capable of inflicting additional injuries upon it. The precise nature of these injuries it is impossible to state at present. I think it likely that this is one of the causes of fatty infiltration of the liver, and it may perhaps be influential in the production of connective-tissue alterations. But although we cannot accurately measure the indirect effect of alcohol, I believe it to be of great importance in relation to human nutrition, and one which exerts a highly unfavourable influence on the prognosis of many kinds of disease. You can readily understand that it is a very difficult matter to separate the factor of disordered digestion from the action of alcohol *per se*.

A good deal might be said about the structural alterations induced by alcohol in the heart and in the blood-vessels, but I shall not undertake to touch on this aspect of the subject. Similarly a long chapter could be written in reference to the pathological action of alcohol on the nervous centres. I shall only remind you of the clearly defined alterations in the chromatin network of the ganglion cells of the brain, which have been repeatedly observed in acute alcoholic intoxication as well as in chronic alcoholism. The important and frequent condition of alcoholic neuritis is one with which you are of course familiar.

I think it unnecessary to multiply examples of the pathological consequences of alcoholic excess. The conditions which I have referred to in this short sketch are of a sufficiently serious character to affect distinctly the comfort and usefulness of the individual, even where they do not actually

threaten life. But the effects of alcohol are by no means limited to the individual who practises habitual excess in drink. Alcohol is capable of poisoning the germ plasm, the carrier of hereditary qualities. In consequence of this the world contains a considerable number of people with nervous systems in various ways weakened from the very beginning through the sins of alcoholic excess committed by one or both parents. This is surely one of the very worst aspects of the drink evil.

I trust that enough has now been said to show you that although alcohol possesses an unquestionable food value the habitual use of alcoholic drinks by healthy persons is an indulgence and a luxury entirely unnecessary either for the growth or the maintenance of the body. It seems to me clear that a small number of people take alcoholic drinks habitually, and in such small amount that it is not possible to discover any injury to their physical well-being. It is only fair to admit this fact, however much one may disapprove of the use of alcohol by healthy persons. On the other hand, I am of the opinion that the majority of persons who take alcohol habitually, even in quantities that cannot be called immoderate in the sense of producing intoxication, eventually suffer injury, though perhaps only slight injury, from its use. This injury to health comes chiefly through chronic gastritis and partly through effects upon the nervous system. In view of this one should discourage the habitual use of alcohol, even its moderate use as an indulgence, for one ought never to lose sight of the fact that its influence is upon the whole more detrimental than helpful, even to cautious drinkers.

Of course it is evident that you will not very often have an opportunity to exercise your influence among healthy persons for the discouragement of what is known as moderate drinking. People are not in the habit of consulting physicians in regard to this practice while they are enjoying health. On the other hand, in your practice you will almost every day be called upon to decide whether it is proper to employ alcohol for its therapeutic properties, and I can assure you that it is no easy matter to make your decisions correctly. Perhaps I can help you to form a judgment as to where alcohol may be used by giving you certain conclusions which I have reached in reference to this difficult question.

In the first place it is necessary to make a sharp

distinction between the therapeutic use of alcohol in acute and chronic diseases. In acute disease there is little or no danger of forming the alcohol habit. In chronic diseases the possibility of forming a habit dangerous both to the physical and moral welfare has to be kept clearly in mind.

In acute disease alcohol may be employed either for its properties as a stimulant or for its nutritive value, or for both these effects. There is little experimental evidence in favour of using alcohol as a cardiac stimulant in febrile disease with flagging heart, but I think that clinical experience justifies its use in many cases of fever. For instance, it appears to me that in the course of pneumonia there often comes a time when the weak and rapid heart action is improved by moderate alcoholic stimulation. I confess that this is merely a clinical impression based on watching the course of many pneumonias. It is possible that the cases would have done as well without alcohol.

This difficulty in forming a decision is one which we meet in many of our therapeutic trials, and is sometimes not a little discouraging to those who wish to establish the truth. Try to form an independent judgment as to the value of alcohol as a stimulant by carefully watching your patients. The temporary use of alcohol as a stimulant after acute gastro-enteric disease appears to me of great value, especially in the case of children and elderly people. One often notes a rapid improvement in appetite and in the force of the pulse when small repeated doses are thus employed. I have no doubt that alcohol often greatly aids in the process of reconstruction after acute digestive disorders with loss of weight and strength.

Clinical experience makes me think that the addition of a small amount of alcohol distinctly favours the timely digestion and absorption of milk. You know that milk has the peculiarity of stimulating only mildly the secretion of the digestive juices. In fevers and in conditions which make necessary a free use of milk, but in which there is an impaired secretion of the gastric juice, and presumably also of the pancreatic juice, the addition to the milk of 1 or 2 per cent. of alcohol gives the patient the benefit of a mild and harmless stimulus to the secretion of gastric juice. I regard the temporary use of alcohol in this way as one of the most legitimate therapeutic uses of alcohol.

The food value of alcohol can be utilised in many acute

and subacute diseases. Thus in all acute and subacute febrile affections there is apt to be a distaste for food, and the digestion and absorption of the ordinary food-stuffs are impaired. The waste of the organism in fat is not replaced fully by the food, and this excessive waste may contribute to occasion considerable loss of weight and strength. Alcohol is so readily absorbed that it is unquestionably a valuable food under these circumstances. It should, however, be used in great moderation and with much caution because of the danger of exciting gastritis. In this way you can safely replace a portion of the fats and carbohydrates which should enter into a dietary. An adult can ordinarily take from 30 to 60 grams of alcohol daily, if well diluted, with little danger of gastritis, but there are persons in whom it is advisable to use considerably less.

In chronic disease, as I have already said, one ought to be most cautious in recommending the use of alcohol. I am absolutely opposed to the use of alcohol as a remedy for mental depression or any form of pain. It is sometimes a most helpful hypnotic of a mild kind, and may occasionally be safely employed to induce sleep; but its use should be only occasional, and the actual cause of the insomnia must be removed by suitable treatment.

Alcohol is frequently recommended by physicians to patients suffering from chronic phthisis. Many of these unfortunate people consume large amounts of alcohol, and I think there is little doubt that so long as digestion is unimpaired by the use of the alcoholic drinks there is a partial replacement of fat by alcohol, and the patient holds his adipose stores better than he would without the use of alcohol. Whether the alcohol saves proteid waste is another question, as I have already explained. But while it is true that the alcohol consumed by chronic consumptives often acts beneficially as a food, it is also true that it has at least two highly important dangers. One of these is the development of nutritive disorders from gastritis, disorders which may ultimately contribute to a rapid failure in health. The other great danger is the establishment of an alcoholic habit, which impairs greatly the intellectual force of the patient, and, what is worse, undermines his moral character. In spite of these dangers I think one is sometimes justified in employing alcohol in chronic phthisis, but you will have to judge for yourselves in each individual

instance whether you are justified in allowing your patient to take the incidental risks. I am unable to give you any rule which you can safely follow in all cases.

There is another class of chronic patients to whom alcohol is recommended very frequently. I have in mind persons whose nutrition has become impaired in consequence of long-continued disturbances of digestion. These patients are distinctly below the normal weight, are easily fatigued, and usually suffer from excessive fermentative and putrefactive processes, perhaps associated with dilatation of the stomach. Since alcohol is easy to take and is readily absorbed, its food value can be utilised by patients of this kind, and often proves a distinct help in adding to the store of fat in the body. I have many times observed an increase in weight after the use of alcohol when ordinary methods of medication had failed. But it is by no means clear that this additional fat in the body is really beneficial, and I strongly suspect that one usually does more harm than good by giving alcohol in these cases by still further impairing digestion. I am therefore opposed to this method of treating states of chronic under-nutrition.

I have by no means said all there is to say either against alcohol or in its favour as a therapeutic agent, but I hope I have made clear, first, that the chief use of alcohol in medicine is dependent on its food value, and secondly, that with few exceptions the prescribing of alcohol entails dangers which more than offset its useful properties. Never forget for one moment that alcohol is very often a food and a poison at the same time.

I regret that time does not permit me to discuss with you the properties of the different kinds of alcoholic drinks. For such information I must refer you to books upon dietetics, although I may perhaps be permitted to remind you of a few well-known facts connected with this subject. Thus it is well to remember that most wines have a percentage of alcohol varying from 7 to 10 per cent., while port, madeira, and the sherries have from 15 to 18 per cent. The organic acids, consisting largely of tartaric acid, vary between 0·4 and 0·8 per cent. in the ordinary wines, and constitute an objectionable feature in the case of some dyspeptics. The extractive matters are low in wines, and the sugar varies widely from a small fraction of 1 per cent. in Moselle and some clarets to more than 10 per cent.

in champagne. The large content of sugar in champagne is what makes this wine so apt to derange digestion in some persons.

Brandy and whisky contain not very far from 50 per cent. of alcohol, and should therefore never be drunk straight. The content of organic acids and sugars in these liquors is very low indeed. This makes it possible for many persons to take a little whisky without apparent detriment who cannot take the same quantity of alcohol in the form of wine without developing gouty or dyspeptic symptoms. Besides ethyl alcohol we find in spirituous liquors other products of fermentation, such as aldehydes and the higher alcohols, propyl, butyl, and amyl. These substances constitute the 'fusel oil,' which gives to the cheap and imperfectly distilled peculiarly detrimental properties.

The ordinary beers, which are representative of the malted liquors, contain only about half as much alcohol as the wines, but have a remarkably high percentage (5–7 per cent.) of extractive substances. These extractive substances consist mainly of dextrin and maltose, and thus impart to beer a very considerable nutritive value aside from the alcohol. Beer also contains from 0·4 to 0·8 per cent. of proteid material, which is mostly in the form of peptone, or, more correctly, albumoses. The supposed diuretic properties of beer are probably due very largely to the volume of fluid taken by beer-drinkers. Although beer is perhaps the least harmful form in which alcohol is taken, it gives rise to all the evil effects of alcohol when taken in excess, including such structural alterations as cirrhosis of the liver and multiple neuritis.

Let me now say a word to you in reference to the organic acids which occur in the food. This subject has a certain relationship to the subject of alcohol, for, as I mentioned to you, alcohol is probably oxidised to acetic acid in the organism before its final oxidation to carbon dioxide and water. Some foods contain organic acids of the fatty acid series in considerable amounts. This is especially true of fruits and some vegetables. You should know something of the destiny of these acids in the organism and of their effects on digestion, for there are many persons who are unable to take them without disturbances, and moreover some persons show very remarkable idiosyncrasies.

Acetic acid (CH_3COOH) occurs in vinegar; butyric acid (C_3H_7COOH) in rancid butter; lactic acid ($C_2H_4{<}^{OH}_{COOH}$) in fermented milk; malic acid $\begin{matrix}(CH)OH).\ COOH)\\ |\\ (CH_2\ .\ COOH)\end{matrix}$ in apples, cherries, and some wines; tartaric acid $\begin{matrix}(CH(OH)COOH)\\ |\\ (CH(OH)\ .\ COOH)\end{matrix}$ in grapes, cucumbers, potatoes, and wines; citric acid $(C_3H_4(OH)\begin{matrix}COOH)\\ COOH)\\ COOH)\end{matrix}$ in lemons, currants, raspberries, and gooseberries; oxalic acid $\begin{matrix}(COOH)\\ |\\ (COOH)\end{matrix}$ in sorrel, spinach, rhubarb, tomatoes, and tea. Of these acids malic and tartaric are dibasic, and citric tribasic. They form acid salts, and are present in the food especially as acid salts of potassium.

Like alcohol, the organic acids of the fatty acid series which I have just mentioned are oxidised in the body to carbon dioxide and water; and, as in the case of alcohol, this decomposition and oxidation is accompanied by the liberation of energy. These acids thus have a food value comparable with that of alcohol. Oxalic acid is burned in the body only to a limited extent.

Most persons in health are able to take these various organic acids contained in fruit and vegetables without exhibiting any harmful effects from the moderate quantities which are introduced into the stomach in this way. The acids are absorbed as acid salts, and on being burned in the body become a source of energy. I am disposed to think that a not inconsiderable portion of the carbohydrates, or fats of the food, may be replaced by organic acids where the state of digestion permits abundant absorption.

I recall very distinctly an experiment which I made some years ago with a young pig. The animal received the same amount of milk as other young pigs in my laboratory, but in addition was induced to take from 50 to 100 c.c. daily of glacial acetic acid well diluted with water. The principal result of this experiment, which extended over many months, was that this particular pig grew much larger than his fellows. I was astonished to find at autopsy an enormous

development of fat with a melting-point lower than that of ordinary hog-fat. I believe this large development of fat was connected with the absorption and utilisation of the large allowance of acetic acid, very little of which reappeared in the urine and fæces of the animal. The possibility of a synthesis of fat from acetic acid is suggested by this experiment.

But while the organic acids of fruits and vegetables are commonly utilised in the way I have just described, there are many persons in whom they create very decided disturbances. These persons usually show some of the indications of chronic gastritis, and are apt, I think, to secrete very little free hydrochloric acid during gastric digestion. Among the symptoms which follow the use of moderate quantities of fruit are a sense of discomfort referred to the stomach, abdominal pain, sometimes amounting to colic, diarrhœa, or in some instances headache. That the symptoms are really due to the organic acids and not to other ingredients of the fruits is rendered extremely probable by the fact that in certain patients the same symptoms can be elicited by giving separately malic or citric, or some other acid characteristic of a particular fruit.

You will find that with many patients it is wise to withdraw fruits and all foods containing considerable quantities of organic acids or acid salts. In other cases it is not necessary to withdraw such food wholly from the dietary, but to restrict it. It often requires a little time and experimentation to determine how much and what kind of fruit is permissible.

I have observed that in most persons who cannot tolerate moderate or considerable quantities of the ordinary fruits there is difficulty about the digestion and absorption of carbohydrates, and am disposed to think that the acids formed during excessive fermentation can often be disposed of without the production of any disturbance, but that the addition of an abundance of organic acids in the food is frequently sufficient to precipitate symptoms under these circumstances.

Your patients will often consult you as to the advisability of using tea and coffee, and it is important to be able to guide them intelligently. You must therefore know something about these widely employed luxuries. The coffee bean from which coffee is prepared contains about 0·7 per cent. of caffein, and as most of the caffein is extracted in the

process of preparing the drink each cup of coffee contains from 0·1 to 0·2 gram (1½ to 2 grains) when the beverage is made of the usual strength. Besides caffein the roasted coffee contains volatile substances known collectively as coffeon or coffeol. These substances are developed by the process of roasting, and have properties resembling those of volatile oils.

Tea differs from coffee chiefly in the following respects: (1) in containing a larger percentage of caffein (1·5 to 2 per cent.); (2) in containing a high percentage (7 per cent.) of tannic acid. Green tea and black tea differ in that the former contains a considerable amount of a volatile oil, which is dissolved in the infusion.

The well-known effects of tea and coffee in exciting a state of wakefulness and in giving a sense of relief from fatigue are doubtless due to the caffein which they contain. The behaviour of caffein in the economy I cannot stop to discuss at present. I will, however, remind you that caffein is closely related in composition to xanthin—is, in fact, a trimethyl xanthin—and that xanthin or xanthin-like substances are found in small amount in the nuclei of animal cells.

In some persons the caffein of tea and coffee leads to an excessive irritability of the nervous system, which is shown by an increase in the excitability of the simple and complex reflexes. Children appear to be especially susceptible to the effects of coffee and tea, and some cases of insomnia and night-terrors are referable to their use. The chronic effects of coffee in excess vary in different individuals. In some persons there arises a depressive form of neurasthenia which quickly improves after withdrawal of the drug. In others a tremor like that of alcoholism is developed, and this tremor may temporarily subside after a cup of strong coffee. In still other persons neuralgic symptoms are prominent.

One other detrimental effect of tea and coffee must not be overlooked. This is that they slow the action of the digestive ferments, both outside and inside the body. In many persons this slowing of digestion from tea or coffee is a matter of no moment, but in others it is a very undesirable thing. I consider it good practice to restrict patients in drinking coffee and tea in all cases where a study of the gastric processes shows that the food is too slowly digested and lingers too long in the stomach, or where the secretion

of free hydrochloric acid is regularly much below the normal.

The peculiar sense of comfort and general well-being which coffee-drinkers experience after drinking coffee with a full meal is ascribed to the volatile substances which it contains, and is certainly not due to the caffein. The increased peristalsis from coffee is also probably due to coffeon. In many persons this effect is found very helpful in facilitating regular movements of the bowels, but in others it causes colicky sensations and diarrhœa. There is another effect of coffee which, though only rarely observed, is sometimes the cause of much annoyance. I refer to intense itching about the anus, due generally to slight eczema. The relation to the use of coffee is clearly demonstrable in some of these cases of pruritus.

In regard to tea one has to remember that it is often steeped too long, and comes to contain much tannic acid. In some instances the amount is so large that it precipitates the albumoses and albumins in the stomach, and through its astringent action on the mucous membrane leads to constipation and chronic gastritis. Many women of the lower orders are inveterate tea-drinkers, and grow thin and nervous from the over-indulgence.

Although the evil effects of tea and coffee are far less serious than those of alcoholic drinks, you will frequently find it advantageous to restrict their use, even where the history told by the patient does not give you the proof that the tea or coffee has been acting harmfully. But while the injurious effects of coffee and tea are less than those of alcohol their utility is also less, since neither of them possesses any food value, and both are simply stimulants of more or less efficacy. It is essential for you to remember this fact, and to impress its truth on those patients who are convinced that tea and coffee act as foods which are capable of 'building up their systems.' Remember, also, that neither tea nor coffee diminishes metabolic activity. On the contrary the evidences of increased metabolism, namely, the augmented output of urea and carbon dioxide, have been observed to follow their use, probably owing to the increased activity induced in the nervous centres. One cannot but smile at the proposition, seriously made by one theorist to the besieged defendants of Paris in 1870, that the soldiers be served with a diet consisting exclusively of tea and coffee.

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LECTURE VI

EXCESSIVE FERMENTATION AND PUTREFACTION IN THE DIGESTIVE TRACT.

The micro-organisms of the digestive tract, distribution and characteristics—Bacterial products: conditions influencing their character—Fermentation and putrefaction—Types of fermentation in the digestive tract: alcoholic, lactic, acetic, butyric—Normal and pathological fermentations—Effects of excessive fermentation—Local effects due to formation of gas or to irritant products—Flatulence—Probable effects of alcohol, acetic, lactic, and butyric acids—Impaired secretion of hydrochloric acid: excessive secretion—Gastritis and excessive fermentation—Effects of excessive fermentation in the intestinal tract: diarrhœa and colic, change in the stools, loss of food potential—Fermentation in the fæces outside the body—Acid products and catarrhal enteritis—Influence of fermentation upon putrefaction—Remote effects of excessive fermentation; subjective symptoms—Alterations in the composition of the urine—Changes in acidity—Frequent micturition—Increased excretion of uric acid—Oxaluria as a consequence of excessive fermentation—Significance of oxaluria—Comparison of fermentative and putrefactive processes in their effect on the composition of the urine.

To-day I invite you to consider with me the fermentative and putrefactive processes that go on in the stomach and intestine. It is no exaggeration to say that if I succeed in giving you a reasonably clear picture of these processes in their pathological relations you will have in your possession the key to an understanding of the disorders of digestion and many disturbances of nutrition. Unfortunately it is hardly possible to do more than outline for you some of the features of excessive fermentation and putrefaction. We are still groping our way to light upon this obscure and difficult subject, and, with the best intentions, I can give you only an imperfect idea of its nature and practical bearings.

There is no good reason to suppose that the presence of micro-organisms in the digestive tube is necessary to life. On the contrary, recent experiments on inferior animals

show that the digestive and other vital processes are carried on effectually without their aid—at least for a time. Micro-organisms are, however, regularly present in great numbers in the human digestive tract. Within the first day of life the alimentary tube of the newly born infant becomes infected, doubtless through the agency of milk, water, or air. Although the tube soon swarms with bacteria, these are chiefly of two varieties during the milk-diet period of infancy—the bacillus acidi lactici and the bacillus coli communis. Just as soon as the growing organism feeds on a general diet the number and variety of the bacterial inhabitants of the gut become greatly increased. Still, even in adult life, the lactic acid bacillus and the many varieties of the colon bacillus are the most important flora. The former is found in the stomach at times, and in the upper part of the small intestine. The different forms of colon bacillus are found widely distributed through the intestine, but are specially abundant in the colon. These bacteria are aërobic, that is to say, they consume oxygen in the course of their life activities. In virtue of this property they act as powerful reducing agents on the intestinal contents. We have an example of this in their effect on the bilirubin of the bile from which they take oxygen, and thus form the urobilin or stercobilin, to which I shall have occasion to refer in another lecture. But please note the fact that these bacteria do not require oxygen for their growth: they continue to live even when wholly deprived of it; they are facultative anaërobes. Moreover, the intestine contains many bacteria that normally live without oxygen. We still know little about them or their influence on decomposition.

Besides bacteria, the upper part of the digestive tract is apt to contain other forms of plant life. The common yeast organisms are often, if not always, found in the stomach, and sarcinæ are frequently present. These are probably to be regarded as accidental inhabitants. They do not normally succeed in establishing themselves.

Although we have no good reason to believe that the presence of micro-organisms in the human digestive tract is essential to the maintenance of life, there is some evidence that these organisms are not without their physiological uses. The absorption of fats is certainly facilitated by the cleavage of the fat molecule into glycerine and fatty acids, which is carried on to some extent by intestinal bacteria.

Probably a much more important use of the intestinal bacteria relates to their effect in destroying foreign micro-organisms which find their way into the digestive tract. It is known that the introduction of many foreign species by the mouth is followed by their disappearance from the fæces soon after the administrations have been stopped. Bienstock found that certain anaërobic bacteria, like the bacillus putrificus and the bacillus tetani, were destroyed in the intestine by the action of the normal inhabitants of the gut, although their spores might reappear in the fæces. It is probable that the bacillus aërogenes capsulatus, the exciter of malignant œdema, is destroyed under similar conditions. Thus it appears that the normal inhabitants of the intestine are capable of exerting a certain protective action against pathogenic bacteria which have escaped the destructive action of the gastric juice. We cannot now say to what extent the normal bacterial species protect the human organism against the products of pathogenic varieties.

The bacteria of the gastro-enteric tract interest us as physicians in two ways: first, through the products which they form in the course of their life activities; and secondly, because they are capable of entering the blood stream after passing the epithelial barrier of the intestine wall. If they enter the blood-stream in considerable numbers they may give rise to a septicæmia which in the case of definitely pathogenic bacteria assumes a serious clinical aspect. Important as these intestinal septicæmias undoubtedly are, they do not especially concern us now. It is rather to the bacterial products within the intestinal lumen that I wish to direct your attention.

The character of the products formed in the digestive tube under the influence of micro-organisms is influenced by a variety of conditions: by the chemical nature of the food, by the nature and number of bacteria introduced with the food, by the quantity and composition of the digestive juices, by the rate of absorption, and by the state of the motor functions of the stomach and intestine. It does not require a highly developed imagination to see how complex must be the conditions which enter into these bacterial activities, and how hopeless is the task of tracing the precise influence of each of these factors. In spite of these difficulties investigators have succeeded in getting some idea of the products of bacterial action in health and in disease.

That the nature of the substances formed by the micro-organisms living in the stomach and intestine should be largely dependent on the chemical composition of the food-stuffs might be predicted. The fats, the carbohydrates, and the proteids are so different in constitution that the substances resulting from their cleavage or decomposition must necessarily be dissimilar. The fats and carbohydrates have at least this in common, that they contain carbon, hydrogen, and oxygen. The proteids, on the other hand, contain not only carbon, hydrogen, and oxygen, but also nitrogen and sulphur. Now this difference is an extremely important one. Its significance lies in the fact that many of the decomposition products of the proteids under bacterial influence contain nitrogen or sulphur. They have thus an entirely different chemical character from the substances that arise from the decomposition of fats or carbohydrates. This difference in chemical composition carries with it important physiological differences, and we may say in a general way that the nitrogen-containing products of proteid cleavage are distinctly more toxic to the organism than products which do not contain nitrogen. Differences like these justify us in employing different words to express the processes that result in the formation of these dissimilar products. Throughout these talks I shall speak of the microbic products of the decomposition of fats and carbohydrates as the result of fermentation, and shall use the word 'putrefactive' in speaking of the processes of proteid decomposition under the action of micro-organisms. This distinction is of course arbitrary. Some writers use the terms 'fermentative' and 'putrefactive' in a different way. I think it convenient to employ them as I have just described, putrefaction referring to proteid decomposition, fermentation to the cleavage in fats, sugars, and starches.

Although fermentative and putrefactive processes go on side by side in a large extent of the digestive tract, we may say that in health putrefaction preponderates in the colon, and that fermentation is unaccompanied by putrefaction during gastric digestion. In disease a slight degree of putrefaction sometimes goes on in the stomach, and in some instances fermentation is very active in the lower part of the intestinal tract.

For the sake of convenience and other practical reasons it will be best for me to tell you something of the different

types of gastro-enteric fermentation before discussing the putrefactive decompositions of food. Having described for you the chief forms of fermentation, I shall say something of the local and remote effects of the substances formed in the course of the process when this grows excessive.

There are four well-recognised forms of fermentation that may begin in the stomach or in the upper part of the small intestine: 1. Alcoholic fermentation. 2. Acetic fermentation. 3. Lactic fermentation. 4. Butyric fermentation. Frequently two or more of these coexist, but it is usual for one to preponderate. I am confident that we ought to recognise another and frequent form, namely, fermentation with the production of oxalic acid.

Alcoholic fermentation occurs in consequence of the presence in the stomach of some form of yeast plant or saccharomyces, together with a sugar. Some bacteria are capable of setting up alcoholic fermentation, but their action in this direction is unimportant. The yeast plants are widely distributed and find their way into the stomach so frequently that some form of yeast may be regarded as a nearly constant inhabitant. As sugar forms a common article of food, some degree of alcoholic fermentation is very frequent and may probably be considered normal. Most sugars are fermented by the ordinary yeast organisms. Lactose, or sugar of milk, is an exception, but is readily broken up by special and less common forms of yeast.

If we add ordinary leaven yeast to a solution of saccharose or glucose, the greater part of the sugar is rapidly broken up into alcohol and carbon dioxide. The decomposition is represented as follows :—

$$\underset{\text{(glucose)}}{C_6H_{12}O_6} + \text{yeast} + H_2O = \underset{\text{(ethyl alcohol)}}{2C_2H_5OH} + 2CO_2 + \text{yeast} + \underset{\text{(carbon dioxide)}}{H_2O}$$

Although most of the sugar is decomposed in this way, a certain amount (about 4 per cent.) goes to the production of other substances, especially lactic acid. If we calculate the yield of ethyl alcohol that would be obtained from the conversion of all of 100 grams of glucose by alcoholic fermentation, we find that it amounts to more than 50 grams. This is a very considerable amount of alcohol, and though it is unlikely that such an amount is ever formed in the human subject in the course of a day, it seems probable that a not unimportant quantity of alcohol may be manufactured

by persons with gastric dilatation who indulge freely in carbohydrates. At the same time carbon dioxide is formed in large amount. I shall remind you of these things when we discuss the symptoms of excessive fermentation.

The yeast plant grows well in neutral or slightly acid media. A percentage of 0·2 per cent. of free hydrochloric acid is compatible with abundant growth. This is important for you to remember, because it means that alcoholic fermentation may continue during digestion in a medium which inhibits the growth of many bacteria. In gastric contents with 0·4 per cent. of hydrochloric acid ordinary bacteria are killed. The saccharomyces are still capable of some growth, but soon lose the ability to produce gas and alcohol. There are conditions of altered secretion of the gastric juice in which the percentage of free hydrochloric acid rises to a point where alcoholic fermentation is checked, but in a very large majority of gastric disturbances alcoholic fermentation is possible.

Since alcoholic fermentation requires the presence of carbohydrates, their withdrawal or diminution is followed by the cessation of this kind of decomposition. But, as the yeast organisms are apt to remain in the stomach even though carbohydrates are withdrawn, the fermentation begins again as soon as sugar is given. The number of yeast organisms in the stomach is probably much reduced by systematic washing of the stomach. We do not know how much alcohol is formed in ordinary derangements of digestion accompanied by the excessive production of carbon dioxide, because other kinds of fermentation also lead to the formation of this gas. Alcohol is so rapidly absorbed that we cannot be sure it has not been produced in considerable amount even when it is not to be detected in the stomach contents. I have several times discovered alcohol in the filtered stomach fluids in cases where there has been gastric dilatation, or where for any reason there has been delayed expulsion of the contents of the stomach.

The second form of fermentation of which I wish to speak is that accompanied by the formation of lactic acid. Owing to its frequency this is a very important type of carbohydrate decomposition. In the normal conditions of the stomach lactic acid is either not formed at all or only in small amounts. Whenever the stomach is unable to empty itself with physiological promptitude, lactic acid fermentation

is liable to be active if carbohydrates are freely eaten. Hence we find considerable lactic acid in the stomach of persons with gastric atony with or without dilatation.

Lactic acid fermentation is induced by many different organisms. The ordinary milk-curdling ferments are short, plump, motionless aërobic cells, united in pairs or in groups of four. The bacillus acidi lactici conforms to this type. Organisms of this character are widely distributed. I believe that in the human subject lactic acid decompositions are generally referable to the bacillus acidi lactici or the bacillus lactis aërogenes, two closely related forms. The colon bacillus is also capable of fermenting carbohydrates with the formation of lactic acid. Moreover, two species of lactic acid-forming micrococci have been found in the saliva and the mucus of the teeth. Thus, you see, the digestive tract abounds in organisms capable of setting up lactic acid fermentation.

The chemical conditions that favour lactic acid fermentation are somewhat different from those friendly to the alcoholic type of decomposition. You know that the addition of yeast to a pure solution of sugar is very promptly followed by the production of gas. The presence of a lactic acid ferment and a sugar solution is not enough to induce active lactic acid production. The presence of proteid material is necessary. Thus, 1 or 2 per cent. of peptone in a sugar solution makes a very good medium. Reduce the peptone and you get less lactic acid and a larger proportion of volatile fatty acids. A neutral reaction is most favourable to the growth of the lactic ferments, but they are said to grow fairly well in the presence of free hydrochloric acid in lesser concentration than 0·7 per cent. Therefore we can say that the conditions favourable to the production of lactic acid—a neutral or slightly acid medium containing sugar and proteid—are almost always to be found in the stomach. But note well the fact that a neutral medium is the most propitious, and that such a medium is often found where there is stomach disease with impaired secretory activity.

The acid produced by most lactic acid ferments is of the optically inactive variety. That is to say, the solutions of the acid do not rotate the plane of polarisation either to the right or to the left. Some organisms, however, produce an acid which is optically active. It is much the same kind of acid in its physiological properties. Thus the colon bacillus grown

on glucose makes an acid which rotates to the right, but, if cultivated in lævulose, yields an inactive acid. Glucoses, saccharoses, and milk sugar are all susceptible of lactic acid fermentation, but the action on milk sugar is slower than in the case of other varieties. The action on the glucose molecule is apparently very simple, the molecule being split into two equal parts; thus: $C_6H_{12}O_6 = C_3H_6O_3 + C_3H_6O_3$. Probably all the sugars are split into dextrose or lævulose before being broken up into lactic acid.

We know little about the actual conditions that lead to the formation of acetic acid in the gastro-enteric tract. Yet acetic acid is found in the stomach contents not very rarely. I have found it especially in cases of dilatation of the stomach, where it has been present in small amount in association with larger quantities of lactic acid. It may also be found in the fæces, where intestinal fermentation has been active.

In the commercial production of vinegar several different bacterial ferments have been employed under the specific name 'mycoderma aceti.' Many of the bacteria normally inhabiting the digestive tract are also capable of making acetic acid. Which ones are especially apt to be engaged I cannot tell you. Nor can I tell you with certainty how the acetic acid of the digestive tract is formed. It is generally supposed to be formed through the oxidation of some partly oxidised member of the fatty acid series, as ethyl alcohol or acetic aldehyde. By oxidation ordinary alcohol (C_2H_5OH) is converted into acetic aldehyde, and, on further oxidation, acetic aldehyde is changed to acetic acid; thus:

Ethyl Alcohol + Oxygen = Acetic Aldehyde + Water

$$C_2H_5(OH) + O = CH_3CHO + H_2O$$

and

$$CH_3CHO + O = CH_3COOH \text{ (Acetic Acid).}$$

It is possible that acetic acid is made only where alcoholic fermentation has occurred. I have several times found alcohol and acetic acid together, but sometimes acetic acid is present when alcohol cannot be detected. The conditions under which acetic acid is made in the digestive tract are certainly worthy of more attention than they have received.

Fermentation with the production of butyric acid is by no means uncommon in the digestive tract. The pungent

odour of butyric acid is so distinctive that it enables us generally to detect the presence of the acid without resorting to chemical manipulations. One notices this odour in the vomited material or stomach washings in most cases of chronic gastritis with the production of an abundance of mucus, and one also observes it in some instances of acute gastritis. Small quantities of butyric acid are often present in the fæces, especially where intestinal fermentation is excessive. The butyric acid is apt to be associated with other volatile fatty acids, especially acetic.

Several different organisms have been described which have the property of producing butyric acid. The one which has been most carefully studied is a strictly anaërobic liquefying bacterium known as the granulo-bacillus saccharo-butyricus immobilis. This micro-organism is very widely distributed, being commonly found in milk, in cheese, in flour, in water, in dust, and in the fæces, not only of human beings, but of many animals. Under favourable conditions this bacillus produces butyric acid in large amount, but in the digestive tract its activity is restricted. Butyric acid fermentation in the stomach doubtless depends on other organisms than the saccharo-butyricus immobilis.

You should know that many substances are capable of yielding butyric acid. Sugars and starches, including insoluble starches, are its chief source, but it may come from tartaric, citric, malic, or mucic acid. Proteids are also thought to yield butyric acid, and it is said that a small amount of proteid material is essential to its formation. In general we may say that lactic acid and all bodies yielding lactic acid are capable of yielding butyric acid. Lactic acid is certainly apt to be an intermediate step towards butyric acid formation. Thus glucose is split into lactic acid, and this in turn gives butyric acid, carbon dioxide, and hydrogen. These relations can be expressed as follows :—

Glucose	Lactic Acid	Butyric Acid	Carbon Dioxide	Hydrogen
$C_6H_{12}O_6$	$= 2C_3H_6O_3 =$	$C_4H_8O_2$	$+ \quad 2CO_2 \quad +$	H_4

Thus you see that the formation of butyric acid from lactic acid is attended by the production of the carbon dioxide gas which is so important an element in causing flatulence. The free hydrogen which is liberated at once unites with oxygen to form water. Butyric fermentation thus becomes

a powerful reducing agent, that is, an agent active in depriving substances of their oxygen.

The butyric fermentation goes on best in a neutral or alkaline medium, but may continue in fluids that are slightly acid. This accords well with the fact that one finds butyric acid fermentation only in the stomachs of persons who have little or no free hydrochloric acid. At all events this has been my experience.

I must remind you in this connection that butter contains a small percentage of butyric acid united to glycerine. In rancid butter this combination of butyric acid has been decomposed by bacteria, and free butyric acid is liberated. A similar liberation of butyric acid may occur in the decomposition of butter or cream in the intestine, and probably in the stomach. Therefore we cannot be quite sure that the butyric acid of the stomach contents has not come from the decomposition of fat, if the subject has recently taken butter or cream. You will nevertheless find cases where you can assure yourselves that the butyric acid has come from the carbohydrate food.

A few minutes ago I referred to my belief that we must recognise a form of fermentation in the digestive tract accompanied by the production of oxalic acid. It is well known that oxalic acid is formed by some bacteria and by moulds, but the experimental production of this acid in the stomach has only recently been accomplished by one of the workers in my laboratory. Dr. Baldwin has succeeded in setting up in dogs what seems to be a kind of gastritis that is accompanied by the formation of oxalic acid in the stomach and perhaps in the intestine. The gastritis was induced by giving the animals very large quantities of glucose or saccharose daily for many weeks. It seems clear that the carbohydrate material is in some way favourable to a considerable production of oxalic acid, perhaps because the fermentative products set up gastritis and check the secretion of hydrochloric acid; but we do not yet know just how this acid is produced. I suspect that the oxalic acid may really come from proteid material. In a few minutes I shall speak to you again of this subject in its relation to oxaluria.

The different forms of fermentation which I have now briefly described to you are to be regarded as normal processes in the digestive tube just so long as they have no

pathological effects, either locally or on the organism at large. It is undoubtedly true that small quantities of lactic, butyric, acetic, and oxalic acids may be produced in the stomach and intestine without working any injury. It is equally clear that when these substances, any or all of them, are formed in large amount, they are capable of doing harm. Still we are unable to say at just what point normal fermentation becomes excessive fermentation. Fermentation is excessive whenever we can clearly see its effects in certain symptoms, or objective signs, or pathological findings. But do not imagine you can exclude the action of excessive fermentation merely because a patient happens not to have the commonest and most obvious sign of its existence—the accumulation of gas in the stomach or intestine.

The form of excessive fermentation in the stomach with which you will most often meet is that in which lactic acid is formed. Lactic acid frequently cannot be detected in the normal stomach contents at the height of digestion, but it is doubtful whether the formation of a small amount is necessarily pathological. Small amounts are often introduced with the food, as in some kinds of bread, in milk, &c. The regular presence of a considerable quantity is pathological when due to fermentation.

The conditions that favour most the occurrence of lactic acid fermentation are apparently those which promote the other kinds of decomposition which I have described to you. They are diminished motor activity of the stomach, dilatation of the stomach, diminution or absence of free hydrochloric acid, and the excessive use of carbohydrate food, especially of sugar.

Let us now consider the pathological effects of excessive fermentation. It is convenient to separate the local effects from those which are more general and less direct.

The local effects of excessive fermentation are due in part to the liberation of gas, in part to the irritative action of other products. The production of gas leads to distension of the stomach, often followed by eructations. The patient is usually conscious of a sense of fulness in the epigastric region, and percussion indicates some distension of the stomach. In many persons the distension leads to nothing more than slight discomfort, but, where the heart is weak and irritable, disagreeable and even alarming cardiac sensations may follow the upward pressure of the stomach. If

the liberation of gas continues abundantly in the intestine, a very considerable degree of abdominal distension is the result. This is sometimes a very trying symptom. After a time the distension is attended by the free passage of gas by the anus, which gives the patient relief. Please remember that extreme distension of the intestine is sometimes apparently the cause of severe abdominal pain. The gas which distends the stomach and intestine is chiefly carbon dioxide, but at times the stomach contains a mixture of carbon dioxide and hydrogen gas. This hydrogen gas comes chiefly from butyric acid fermentation.

It has been contended that over-distension of the stomach by gases resulting from fermentation is a cause of motor insufficiency. It is difficult to prove to what extent the gas impairs the capacity of the stomach to carry on the motions which lead to the churning and expulsion of the food. The state of the innervation of the stomach walls is perhaps the most important element in determining the motor efficiency of the stomach; but I think it probable that frequent over-distension distinctly aids in reducing the motor power of the organ. Thus the gas formation may be indirectly accessory to the development of dilatation. It is said that pyloric cramp is sometimes a consequence of over-distension of the stomach, and that this cramp favours the undue retention of food within the organ. Possibly this is so, but I question whether it is a really important element in the causation of disease of the stomach.

The influence of the products of excessive gastric fermentation upon the stomach has never received the attention it deserves. That alcohol is capable of setting up what we call a catarrhal gastritis is well known, but it is far from clear that alcohol is ever formed in sufficient amount from fermentation to occasion even slight gastritis. Neither have we positive information in reference to the individual action of lactic, butyric, acetic, or formic acid. We know that each of these acids is capable of acting as an irritant, and of thus impairing the normal secretory functions of the epithelia of the gastric mucous membrane. Even in presumably normal stomachs these acids, and especially butyric and formic acids, are capable of setting up a distinct disturbance of function, inclusive of impaired secretion of free hydrochloric acid. In persons who already have an acute or chronic gastritis even very small quantities of these acids

are capable of giving rise to local pain or to an increase in local pain or discomfort, probably with further depression of the secretory functions of the cells. I should tell you, however, that experiments on pigs and on dogs, made in my laboratory, show that healthy animals are capable of taking very large amounts of acetic acid and of lactic acid for months at a time without any obvious disturbance in gastric function.

The influence of the products of excessive fermentation on the secretory activity of the human stomach is apparently not always the same. We may say that, as a rule, the persistence of excessive fermentation for a long period of time is followed by a diminution in the quantity of free hydrochloric acid that is secreted. I have very frequently found such a diminution in cases where the symptoms or signs of excessive fermentation have been long continued. In this connection it is of some interest that we have succeeded on two occasions in giving rise to what is apparently a mucous gastritis in dogs by prolonged feeding on meat and excessive quantities of sugar. In these cases there was an absence of free hydrochloric acid at the time of the acute gastritis. What products of fermentation are responsible for the repression of hydrochloric acid secretion I am unable to tell you. Perhaps some of the organic acids are responsible. In one of the experimental cases I found formic and butyric acid, but no acetic acid. It is possible that some bodies are concerned of whose presence we are entirely ignorant.

There are cases of excessive secretion of free hydrochloric acid in the human subject that appear to be closely related to an increased degree of carbohydrate fermentation. Thus we sometimes find patients who, on a diet greatly restricted in carbohydrates, have a normal content of free hydrochloric acid, but who promptly secrete an excess of this acid when they take carbohydrates freely. Such persons again show a return to a normal secretion of acid on being cut off from carbohydrates. Perhaps different fermentation products are here implicated than in cases where the hydrochloric acid is deficient, but it is also possible that the same irritants are capable of checking or exciting the secretion of hydrochloric acid according to different and little-understood susceptibilities of the secretory nervous mechanism.

I think we are fully justified in believing that many cases of chronic gastritis are dependent on excessive fermentative activity in the stomach. It seems to me that my experiments

in the production of acute gastritis in normal dogs, by merely giving a large excess of sugar together with meat, indicate that the factor of erroneous feeding is quite sufficient to excite this condition. Clinical experience certainly proves that gastritis may be excited in this way both in children and adults. In the case of children we sometimes have an opportunity to trace the acute gastritis directly to excess in carbohydrates; in adults the conditions are usually more complex, both as regards the nature of the food and the presence of other factors than diet.

It has been suggested that the occurrence of gastric ulcer is favoured by fermentative disturbances, possibly through exciting the excessive secretion of free hydrochloric acid, which, as you doubtless know, is commonly present in gastric ulcer. While such a possibility cannot perhaps be denied, it does not strike me as a probable view.

I have now described to you some of the effects of fermentative processes on the functions of the stomach. Let us see what derangements of intestinal function can reasonably be ascribed to them. The intestinal distension due to the formation of carbon dioxide I have already mentioned. The derangements due to the formation of irritative products, such as fatty acids, lactic acid, &c., are less easy to trace than in the case of the stomach, because the fermentative decomposition is almost always associated with putrefactive decomposition, which is in itself capable of yielding irritant substances.

There are, however, three clinical features of excessive intestinal fermentation besides flatulence which deserve our notice. These are, first, diarrhœa and colic from excessive production of acid; secondly, changes in the appearance and character of the fæces, not including diarrhœa, due to the excessive production of gas and of acid; and thirdly, a loss in weight and in strength dependent on a loss of food potential.

That diarrhœa may be a consequence of the presence of an excessive amount of acid in the intestine is indicated by the result of clinical experience with the therapeutic use of lactic acid, which has often caused diarrhœa. The acid which I have most often found in diarrhœal discharges after the excessive use of carbohydrates is acetic acid. I have, however, made only a few observations on this subject, which is certainly worthy of further study. Butyric acid is probably another agent capable of causing diarrhœa. It

is not surprising that an organic acid like acetic acid should be capable of setting up active peristalsis and of clearing out the contents of the intestine.

The accumulation of small bubbles of gas in the intestinal contents gives rise to an alteration in the colour and consistence of the fæces in cases where there is excessive carbohydrate fermentation. The fæces are soft, often more soft than is normal, in consequence of the admixture with gas. This soft consistence of the fæces sometimes helps to secure free movements of the bowels in persons who become constipated when fermentation is less excessive. In consequence of their gas content the fæces float on water. The admixture with gas causes also a change in colour. Instead of being dark brown the movements are light brown or even yellow. At first sight it may appear as if the stools were deficient in bile-colouring matter, but this is not necessarily the case. If you have ever watched the making of molasses candy, you can easily understand the change in colour that is brought about by the admixture of air. Molasses is dark brown at the beginning, but on being ' pulled ' grows lighter and lighter, and finally becomes light yellow. The phenomena of colour change in the case of the fermented fæces, though less agreeable to think about, are very similar in nature.

The third effect of an excessive fermentation of carbohydrate food—loss in nutritive potential—is an important one if long continued. An adult human being ordinarily consumes 300 or 400 grams of carbohydrate material in twenty-four hours. You will remember that I told you the caloric value of one gram of carbohydrate is 4·1 calories. The caloric yield from, say, 300 grams of carbohydrate is thus about 1,200 calories, or nearly one half the total requirements for twenty-four hours. Suppose, now, that owing to excessive fermentation one third the potential caloric value of the carbohydrate nutriment is destroyed through the conversion of sugar or starch into carbon dioxide and fermentative products of low caloric value, such as acetic acid, lactic acid, &c., which are only partially absorbed. This hypothetical caloric loss is so considerable that it is necessary for the subject to eat an increased amount of fats or proteids to save his tissues from waste. Frequently it happens that, owing to the simultaneously disturbed digestion of proteids, it is not possible to fully

compensate the loss through fermentation by means of an increased use of proteid and fat. Consequently the patient lives to some extent on his tissues in order to meet the caloric requirement. Hence he loses weight and strength. This is, I believe, a very common cause of under-nutrition. It is true that the excessive decomposition of proteid often contributes to this result. Excessive decomposition of fats by bacteria leads to the production of fatty acids in excess, but these may be absorbed and utilised. Thus it is mainly to the carbohydrate and proteid losses that we have to refer the decline in weight that accompanies prolonged fermentative disturbances. An accurate calculation of the loss of food potential incurred in disease in consequence of excessive fermentation is impracticable.

I is of some interest to know that the fermentative process begun in the intestine continues actively outside the body. This fermentation outside the body has been carefully studied. It has been found desirable to distinguish rather sharply between the fermentative process which represents the continuance of the decomposition of sugars, starches, and cellulose, begun in the digestive tract, and that later decomposition which begins after about two days. This late fermentation apparently has no clinical significance. It is a putrefactive as well as a fermentative process. The early fermentation, on the other hand, gives us some information as to the nature of the decomposition in the intestinal tract. The chief feature of this early fermentation is the formation of a considerable quantity of gas with increasing acidity of the fæces. The gas consists of carbon dioxide, methane (CH_4) or marsh gas, and free hydrogen. These three gases are present usually in proportions that do not differ very widely from 17 : 4 : 1 respectively. The carbon dioxide is thus present in great excess. The acids formed are chiefly butyric and acetic, sometimes one, sometimes the other preponderating. Apparently the acids formed are the same as those produced while the fæces are still in the intestine. Small quantities of sulphuretted hydrogen (H_2S) may be formed, and there may be some indol and phenol formation, but these are features of secondary importance. The early fermentation usually ceases, or greatly diminishes, after the lapse of two days. It is not yet clear to me that the study of the fæcal fermentation outside the body is likely to prove distinctly helpful for clinical purposes.

There are two questions connected with the influence of excessive fermentation on intestinal digestion which will very probably suggest themselves. First, may an excess of acid products occasion catarrhal inflammation of the small intestine? Secondly, what effect on intestinal digestion is exerted by the excessive acidity of the intestinal contents? I am unable to inform you satisfactorily on these important points. We have no direct evidence that the organic acids formed during excessive fermentation are the cause of intestinal catarrh, but are justified in suspecting that the irritants known to be capable of setting up diarrhœal stools are also capable of setting up various grades of what we call catarrhal inflammation, *i.e.* of inflicting injury on the epithelial structures of the intestine. It is probable, however, that the effect produced by these acids is often exerted in association with irritants resulting from excessive putrefaction.

As regards the effect of the organic acids on pancreatic digestion we know very little. It has been claimed that an excessive acidity of the intestinal contents operates to check putrefactive processes. It is perhaps true that this is so, but I know of no good evidence of it. We know that excessive intestinal putrefaction is not incompatible with excessive fermentation, if we may judge by the ethereal sulphates of the urine, the indican, the phenol, &c. It is indeed possible that by checking or slowing the action of the pancreatic ferments, which act best in an alkaline medium, the decomposition of proteid food is distinctly favoured. The conditions are so complex that it is not singular our knowledge of what occurs in the human subject should be so restricted.

I wish now to consider with you the more remote effects of excessive fermentation—effects manifested chiefly by certain symptoms of a general character, and by alterations in the composition of the urine. The loss of caloric potential from excessive destruction of carbohydrates we have already considered in its relation to the nutrition of the body.

As regards the subjective state of the patient we are as yet unable to distinguish clearly between the effects of excessive fermentation and excessive putrefaction. Many persons who have the objective evidences of excessive fermentation of carbohydrates—abdominal distension, escape of large amounts of gas, active formation of gas and acid in the fæces, &c.—have also headache, or drowsiness, or mental

depression, or general malaise when they have indulged freely in carbohydrates. How these symptoms are brought about we do not know, and it seems almost idle to speculate as to their origin in the present state of our knowledge. We cannot even be certain that they are due to the products of fermentation as distinguished from those of putrefaction, because, as I have already suggested, excessive decomposition of sugar and starches may indirectly favour the excessive decomposition of proteids. We could perhaps make some inference on this subject by a careful study of the relation between the nature of the food and the content of the urine in putrefactive products, but such observations, carefully conducted, are still wanting. It appears to me probable, however, that the products of excessive fermentation are capable in themselves of inducing effects of the kind I have mentioned, namely, headache, drowsiness, and depression. These effects are most often observed in persons who have long been troubled with fermentative disturbances. Which products are involved it is of course impossible to say. One thinks naturally of the fatty acids, lactic acid, and alcohol. But we know that the fatty acids, such as acetic and formic and butyric, are readily burned in the body, and that only a small part of the acids absorbed are found again in the urine. The same is true of lactic acid. These various acids when absorbed either are burned into CO_2 and H_2O or are neutralised by bases such as sodium and ammonium and appear as salts in the urine. It is certainly an open question whether these unburned acids are capable in small quantities of acting in the human system so as to cause functional derangements. One has to remember that they do not reach the nervous system as free acids, but as salts, and that hence we should expect relatively little disturbance to arise. Where alcoholic fermentation is active it is possible that enough alcohol is formed and absorbed in some instances to occasion drowsiness. You know that the influence of alcohol in bringing on drowsiness varies much with individual susceptibility, and that we occasionally see persons in whom small doses of alcoholic drink occasion slight somnolence. There is no proof that alcohol is ever formed in sufficient amount in the digestive tract to be a cause of the mental hebetude and drowsiness which are not uncommon in persons with fermentative disturbances. Still the possibility that this is so deserves further attention.

Excessive fermentation in the gastro-enteric tract, if long continued, appears to me to be an important factor in bringing on various nervous symptoms belonging to the category of neurasthenic derangements. As a rule, neurasthenic persons give indication of excessive putrefactive decomposition as well as excessive fermentation, and I shall postpone what I have to say on the relation of neurasthenia to these processes until we have discussed the chief types of putrefactive decomposition in the digestive tract.

Among the remote effects of excessive fermentation are certain alterations in the composition of the urine. The alterations include changes in the acidity of the urine, an increase in the uric acid of the urine, the presence of volatile fatty acids such as acetic, formic, &c., and the presence of considerable amounts of oxalic acid.

The acidity of the urine in states of excessive fermentation is sometimes normal, sometimes increased, and sometimes diminished. Why the acidity is increased at times I am unable to explain to you satisfactorily. The acidity of the urine depends, as you know, on the presence of acid salts, especially the acid phosphates and the acid sulphates. The increased acidity of the urine appears to be associated with an increase in the amount of these acid salts. It may be that when organic acids, like acetic and formic, are absorbed from the intestine in such amounts that there is an appearance of formates and acetates in the urine, a portion of the sodium or potassium which would ordinarily go to form neutral phosphates and sulphates is diverted for the neutralisation of the acetic and formic acids. Such a diversion of these bases would diminish the quantity of neutral phosphates and sulphates, and correspondingly increase the proportion of the acid phosphates and sulphates. This would, of course, cause an increase in the acidity of the urine. I find some experimental support for this explanation in observations made on pigs that were fed either on large amounts of sugar or were given very large doses of acetic acid. In each instance the urine, which is normally neutral or slightly acid, became markedly acid, and salts of the volatile fatty acids were found in the excretion. It is also true that in persons whose urine is excessively acid, and who show the signs of excessive fermentation, the withdrawal of bread, potatoes, sweets, and fruits is often quickly followed by a fall in the acidity of the urine. It would be

interesting to know more of the behaviour of the fatty acids in such cases; but the conditions determining the acidity of the urine are much more complex than I have indicated, and I wish you to understand that I regard my explanation as representing only one factor in the production of excessive acidity of the urine. Let me remind you, in passing, that whatever causes greatly concentrated urine causes an increase in acidity. If, therefore, fermentative products cause diarrhœa, a highly acid but concentrated urine is one result. The excessive acidity may thus be due entirely to the unusual concentration.

The low acidity of the urine which we sometimes observe in persons suffering from fermentative excess in the digestive tube is probably to be explained, in some instances at least, by the formation of carbonates. You know that the organic acids are burned in the body with the formation of water and carbon dioxide. Now a part of this carbon dioxide may escape as such from the lungs, but another portion, perhaps, unites with ammonium to form ammonium carbonate, and increases the alkalescence of the blood. This would have the effect of rendering the urine less acid. It may also be that excessive carbon dioxide in the gut leads, on being absorbed, to a diminution in the acidity of the urine. It is very easy to satisfy ourselves of the influence of an excessive amount of intestinal carbon dioxide on the reaction of the urine. If you take a normal dog that is making an acid urine, and pass a current of pure carbon dioxide into his stomach for an hour, you will find that at the end of this time the reaction of the urine is no longer acid, but neutral, or even alkaline. The same effect can be obtained in a somewhat different way. Give the dog a strong solution of cane sugar, to which you have added an ordinary brewer's yeast cake. In a short time the urine will be found to be neutral. I cannot explain these observations

The suggestion that an unusual amount of carbonic acid in the blood influences the urine through the elimination of ammonium carbonate is in opposition to my observation that the introduction of CO_2 into the stomach was not followed by an increased elimination of ammonia. On the other hand, I have known the administration of cane sugar and yeast to a dog to be followed by the appearance of carbonates in the urine.

The degree of acidity of the urine is probably the

outcome of the operation of several different factors, of which I have mentioned only two possible ones. These two factors —the formation of acetates, formates, &c., and the formation of carbonates in the blood—are perhaps capable of antagonising each other.

It must be clear to you that the acidity of the urine in pathological conditions is a subject that urgently demands careful investigation.

You will notice that many of the patients, in whom there are distinct evidences of fermentative excess, pass their urine more frequently than normal. Instead of emptying the bladder four or five times in the day, they do so seven, or eight, or ten, or even a dozen times. I used to think this depended on the presence of an excessively acid urine, and you will, indeed, find that an exaggeration of acidity of the urine is a common accompaniment of this symptom. The mere administration of an alkali will relieve the symptoms in such cases. There are, however, not a few exceptions. The irritation of the bladder that leads to frequent micturition may arise from various causes connected with the composition of the urine, and of these the acidity is only one. What peculiarities in the make-up of the urine are capable of exciting the bladder to more numerous expulsive efforts it is not entirely clear. I have noticed that this irritability, traceable to digestive disorder, may coexist with a neutral urine, and in this connection have been interested in the observation made in my laboratory that dogs can be made to pass urine very frequently by feeding them on sugar and yeast. An excessive carbohydrate meal has a similar effect on some persons. Whether putrefactive products, such as phenol-sulphuric acid and indoxyl-sulphuric acid, have this effect when present in the urine in excess I cannot tell you, but I suspect that these bodies may act as irritants to the bladder.

An increase in the excretion of uric acid, as compared with the total nitrogen of the urine, occurs in some patients after the excessive use of carbohydrates, and appears to be connected with excessive fermentation. I suspect the effect to be an indirect one, in the sense that the fermentative products excite slight gastritis, and that the gastritis leads in some obscure way to the increased production of uric acid from the excessive katabolism of cell nuclei. It seems likely that the gastritis acts so as to derange digestion with

the formation of putrefactive as well as fermentative products, and that the absorption of these substances leads to the abnormal breaking down of cell nuclei. I hope to make this matter clear when we discuss the so-called 'uric acid diathesis.' At present I ask you only to remember that in many persons, especially persons with chronic gastritis, the use of sugar and starches in abundance is followed by obvious digestive disturbances associated with the excessive excretion of uric acid.

As regards the presence of the salts of the fatty acids in the urine we have very few facts. I have found acetates and formates present in the urines of persons who have markedly excessive fermentative derangements. These observations are, however, not free from error, because fatty acids are apt to be found even in the early stages of the decomposition of the urine outside the body and before the reaction has become alkaline. Only when quite fresh urine is used can we feel sure that our results are reliable.

I have already intimated to you that oxalic acid appears in the urine as the result of fermentative processes in the gastro-enteric tract. While it is only fair to say that such an origin has been suspected by some writers on the subject of oxaluria, the first positive proof that the oxalates of the urine may arise in this manner was furnished by Dr. Helen Baldwin, working in my laboratory. After many disappointments Dr. Baldwin succeeded in producing experimentally in dogs a state of pronounced oxaluria. The animals were fed on meat and on large quantities of cane sugar or glucose until a state of excessive fermentation, accompanied by gastritis, was induced. At the time when the oxalates were most abundant in the urine there were distinct indications of acute or subacute gastritis. The gastric contents then contained oxalic acid, and it was possible in some instances to induce a considerable production of oxalic acid by inoculating a medium of sugar and albumoses with material from the gastric contents. As beef contains the merest traces of oxalic acid, and cane sugar contains none, it is clear that the oxalates of the urine cannot have been derived from oxalates preformed in the food. I consider it clear that human oxaluria may arise during carbohydrate decompositions in the digestive tract under conditions at present imperfectly understood, for there are cases where oxalates continue to be found in the urine long after the

patient has ceased to take food containing oxalic acid. Permanent diminution or absence of free hydrochloric acid in the stomach contents appears to be a condition favourable and perhaps essential to the development of this fermentative oxaluria. Perhaps the presence of a small amount of proteid is also necessary.

But I wish to avoid giving you the impression that an abundance of oxalates in the urine can arise in no other way than through excessive fermentation. Any person who eats freely of articles such as tomatoes, spinach, rhubarb, &c., which contain an abundance of oxalic acid, is liable to have a considerable amount of oxalic acid in his urine. Some writers have, indeed, erroneously ascribed all oxaluria to this cause. It seems to me likely that in many instances the oxalates in the urine are due both to their presence preformed in the food and to their formation by fermentation or putrefaction. If the oxalates are present in the urine after removing the articles of diet that contain the oxalic acid, you may feel sure that you are dealing with a case of fermentative or putrefactive oxaluria. You will find that most patients get rid of their oxaluria very quickly on a diet consisting largely of milk.

Since it is true that the oxalic acid which occurs in the food may be a source of oxalates in the urine, you will not unnaturally ask what pathological significance is to be attached to the occurrence of oxalate crystals in the urine. I cannot enter upon the discussion of this subject as I should like to do if the time allotted to us were longer. I shall tell you only the conclusions I have reached without entering into detail as to my reasons for reaching them. A small number of crystals of oxalic acid in the sediment usually has no pathological significance. An abundant precipitate, occurring regularly, indicates the presence of more oxalate of lime in the urine than is usual on an ordinary mixed diet. If the patient is taking only a moderate amount of oxalic acid with the food, it is probable that the abundant separation of crystals indicates an additional cause of oxaluria—namely, carbohydrate fermentation. But you cannot be certain of this unless oxalates are present in the urine after the patient has ceased to have them in the food for five or six days. The appearance of oxaluria during excessive fermentation points to chronic gastritis or to acute or subacute catarrhal processes in the gastro-enteric tract. To

these catarrhal disturbances and their effects on intestinal fermentation and putrefaction we may rationally attribute the depression of spirits which is often noted in persons who habitually have an abundance of oxalates; but we have no good reason to suppose that any symptoms are referable to the action of the oxalates on the nervous system. The flow of urine may be increased by the irritative action of the oxalates on the kidney; but this is probably an exceptional effect. Of course, the separation of oxalates leads often to the formation of calculi in the bladder; but as we are not now especially concerned with the mechanical consequences of oxaluria I shall merely refer to this result.

We have now reviewed some of the leading facts relative to the chemical nature and clinical consequences of excessive fermentation in the gastro-enteric tract. While many of the things I have told you are generally known, I have perhaps been led to dwell on the subject more especially as it appears to me in the light of personal experience. I am clearly conscious of having touched but superficially on the problems connected with the pathology of excessive fermentation, but trust that what I have told you may be of some practical service, and may aid you in thinking about certain clinical phenomena, perhaps with the result of adding to our knowledge.

The putrefactive processes that go on in the digestive tube are of even greater importance to the organism than the decompositions that occur in the carbohydrates. The products of fermentation are for the most part harmless unless they are formed in considerable amount. The products of putrefaction are more likely to be harmful, because, as I have already explained to you, these products consist in part of toxic nitrogen-holding or sulphur-holding substances. A moderate amount of putrefactive decomposition is, of course, entirely normal, and may even be useful in helping the process of peptonisation. We can draw no sharp line between the moderate putrefactive activity on the part of bacteria which we can safely call normal, and the excessive activity which is clearly pathological. You might suppose that the clinical conditions would enable one to form a decision on this point, and very often this is the case; but it is by no means always so. A robust individual may for some time show chemical evidences of excessive intestinal putrefaction, without having any symptoms that can clearly

be referred to the process. Ultimately he develops unequivocal symptoms, but there may be a considerable period in which your only guide in deciding whether putrefaction is normal or excessive is to be found in the amount and character of the products themselves. Fortunately we can learn much about these from a study of the urine.

You may, perhaps, have remarked that the condition of the urine is not of the first importance in detecting the products of fermentative activity, and that, although the urine does teach us something, the state of the stomach contents is far more important. The fermentative processes begin in the stomach, and we can without any difficulty get at the contents of this viscus and determine the nature of the fermentation. The urine does not help us more because of an obvious but important fact, namely this, that the products of excessive fermentation—alcohol, acetic acid, lactic acid, &c.—all belong to the fatty acid series. Now the products belonging to the fatty acid series are more or less readily burned in the body to carbon dioxide and water. Hence they do not to any considerable extent pass into the urine to tell us of what is going on in the digestive tube. The conditions are very different in the case of the products of excessive putrefaction. The putrefactive processes, as you are well aware, go on in the intestine, the stomach being only exceptionally the seat of putrefactive decomposition. We cannot get at the contents of the intestine at the place where putrefaction begins and is most active. We have therefore to rely chiefly on the urine, and we are indeed able to depend on it for the information we need. This is owing to the fact that very many of the products of putrefaction contain an aromatic nucleus, or at least a modified aromatic nucleus. This is, of course, due to the chemical nature of the proteid molecule, which readily yields aromatic bodies or bodies containing modified aromatic nuclei. But as the carbon atoms of the benzol ring and its derivatives are very closely united, the ordinary cellular activities of the body are incapable of disrupting the aromatic nucleus. As a result of this many aromatic bodies appear in the urine in connection with intestinal putrefaction, and serve as important indices of the character of the proteid decomposition in the intestine.

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LECTURE VII

EXCESSIVE FERMENTATION AND PUTREFACTION IN THE DIGESTIVE TRACT (*continued*).

The ethereal sulphates as evidence of intestinal putrefaction—Union of phenol, kresol, indol, and skatol with sulphuric acid—Amount of ethereal sulphates excreted in health and disease—Importance of the ratio of ethereal and preformed sulphuric acid—Evidence that the ethereal sulphates are derived from putrefactive decomposition of proteids in the intestine—Observation of Baumann—Intestinal disturbances and excessive putrefaction; influence of constipation and intestinal occlusion—Increase of ethereal sulphates due to putrefaction outside the gut or to use of aromatic drugs—Toxic action of aromatic products; influence of conjugation with sulphuric acid—Disappearance of preformed sulphates in poisoning by carbolic acid—Glycuronic acid—Phenol and kresol—Indol and indican—Wha- constitutes an excess of indican—Clinical states attended by excest sive indican in the urine—Probable influence of diminished secretion of hydrochloric acid and of the bile and pancreatic juice—Influence of the colon bacillus group—Toxic properties of indol; personal observations—Other products of proteid decomposition—Aromatic oxyacids—Hydrogen sulphide; conditions favouring its production—Cystinuria—Alkaptonuria—Neurin and cholin—Distinctions between septicæmias and intoxications of gastro-intestinal origin—Botulism—Treatment of excessive fermentation and putrefaction in the digestive tract—Importance of hygienic measures—Intestinal antiseptics.

This morning I intend to tell you something about the different types of putrefaction that occur in the human intestine, and also something about the relation of these different kinds of putrefaction to various symptoms of disease. Having done this I propose to sketch for you the therapeutic measures that should be taken to secure a reduction in the intensity of the fermentative and putrefactive processes in the digestive tract.

At our last meeting I intimated to you that we had entered upon the examination of an obscure and difficult field of knowledge. I wish to repeat what I said on

that occasion because it seems to me essential for you to realise that we are travelling on what is still virtually *terra incognita*. It is essential to realise that our ideas of the processes I am sketching for you are crude, incomplete, and destined to undergo considerable development in the course of further research. And I may say that I know of no field in experimental medicine that is more likely to repay intelligent investigation with a richer harvest of practical results.

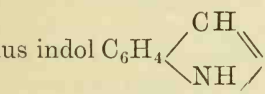
The best index of the extent of intestinal putrefaction that is known to us at present is to be found in the ethereal, combined, or aromatic sulphates of the urine. These sulphates result from the combination of sulphuric acid with aromatic substances formed in the intestine and absorbed from it. Now, as these aromatic substances result from putrefaction of proteid in the intestine, the total amount of ethereal sulphates which appear in the urine is roughly indicative of the amount of the aromatic putrefactive products.

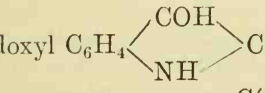
The sulphuric acid in the urine exists only in part as ethereal sulphates; the greater portion of the acid is present as neutral salts of the alkalis, sometimes in part as acid salts of the alkalis. In studying the putrefactive processes in the urine it is important to know not merely how much sulphuric acid is combined with aromatic substances, but also how much is present in the form of the salts of the alkalis—preformed sulphates as they are sometimes called. If we know the quantity of preformed sulphates and also the quantity of the ethereal or aromatic sulphates, we have the advantage of obtaining the proportion which exists between the two, and this is a help in deciding whether or not there is an excessive degree of putrefaction in the intestine.

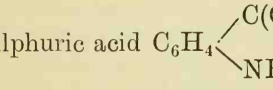
The preformed or neutral salts of the urine hold sulphuric acid which is derived in part from the food, but chiefly from oxidation within the cells of the sulphur belonging to the proteid constituents of the cells. This sulphuric acid is, therefore, an index of the intensity of metabolism, in the same way that the urea of the urine indicates the activity of cell metabolism. As might be expected the sulphuric acid of the preformed sulphates runs nearly parallel to the nitrogen of the urine. In amount it varies from one to three grams daily.

The sulphuric acid in aromatic or ethereal combina-

tion occurs chiefly in union with four different aromatic products of putrefaction. These are phenol and kresol, indol, and methylindol or skatol. Phenol sulphuric acid is $C_6H_5O.SO_3.OH$; kresol sulphuric acid is $C_7H_7O.SO_3.OH$. As indicated by these formulæ both phenol and kresol combine directly with sulphuric acid. The case is different with indol and skatol. Here the synthesis with sulphuric acid does not occur until a process of oxidation has occurred.

Thus indol  is first oxidised to the radicle

indoxyl  before the formation of indoxyl-

sulphuric acid  . In a similar way

methylindol or skatol is oxidised before conjugation with sulphuric acid to form skatol sulphuric acid.

Besides these four aromatic combinations with sulphuric acid there are others less well understood which probably occur in the urine in smaller amounts. The ethereal sulphates are thus dependent on the presence in the urine of a number of different aromatic substances which vary individually in quantity and in their total amount. The total amount of the ethereal sulphates present in the urine in twenty-four hours varies considerably in health—so considerably indeed that it is very difficult to state arbitrarily what are the normal limits. From my experience I should be inclined to say that in an adult the amount is seldom less than 0·12 gram, and not often more than 0·3 gram. In children, especially in very young children, the amount is much less. In disease the quantity is often considerably larger than 0·3 gram, and may reach 0·5 gram or 0·6 gram. Without special analytical procedures it is impossible to say in what proportion the different aromatic bodies contribute to hold the total amount of ethereal sulphuric acid, and such procedures are entirely out of the question for clinical purposes. Thus you perceive that a knowledge of the amount of sulphuric acid in ethereal combination gives us no clue to the specific nature of the putrefaction that is going on within the intestine,

since it does not tell us what aromatic bodies are being formed. On the other hand, it affords an excellent general index of the degree of the putrefactive processes. It requires some technical skill to determine the ethereal sulphates with accuracy, but I advise you to learn how to make such determinations if you propose to practically acquaint yourselves with the disorders of nutrition.

In trying to form an opinion as to whether the ethereal sulphates are increased or not it is necessary to know not merely their total amount, but their proportion to the preformed sulphates, or to the total sulphuric acid of the urine. In fact, I consider the ratio even more important than the absolute amounts.

In health the proportion of the combined to the preformed sulphuric acid varies from 1 to 10 to 1 to 16 in adults on a mixed diet. These figures, though somewhat arbitrary, are not far from the truth. In conditions of disease the proportion often rises to 1 to 7 or 1 to 5, and sometimes the amount of the ethereal sulphates is greater than the amount of preformed sulphate.

But what evidence have we that the ethereal sulphates of the urine are actually derived from the putrefaction of proteid substances in the intestine? I can best make this clear by indicating to you the historical development of our present ideas. It was once thought that the ethereal sulphates are derived from the food in much the same way that the hippuric acid of the urine has its origin in the food. While it is true that vegetable foods contain small amounts of material capable of yielding ethereal sulphates, the ordinary food of man can furnish only a very small portion of the aromatic sulphates found in the urine.

This view of the ethereal sulphates was abandoned in favour of the belief expressed by Salkowski that one of the important ways in which the ethereal sulphates arise is through their formation in the tissues of the body. The facts which seemed to give support to this idea were, first, that the urine in starving animals often contains large amounts of indoxyl-potassium sulphate, recognisable as indican; secondly, that the ethereal sulphates in starving dogs do not disappear from the urine; and, thirdly, that the indican of the urine is often increased in cases of chronic inanition in human beings. It is of course easy to see how these facts might be interpreted to support the theory of the formation

of the aromatic sulphates outside the alimentary tract—that is, in the tissues themselves. But the classical observations of Baumann soon put an entirely new face on the question. These observations were made upon a patient who for many weeks passed the intestinal contents through a fistula in the upper part of the small intestine. Baumann found that during the entire period in which the intestinal contents were diverted through the fistula there was a remarkable diminution in the amount of the ethereal sulphates in the urine, indol, phenol, and the aromatic oxyacids being present in mere traces. As soon as the fistula was closed a pronounced increase occurred in the amount of the ethereal sulphates excreted by the urine. The interpretation very properly given these results was that the occurrence of putrefaction in the contents of the intestine is the cause of the production of the ethereal sulphates, these substances appearing in the urine when the fæces are passed by the anus because of the opportunity then given the intestinal mucous membrane to absorb whatever putrefactive products are found in the gut, but disappearing very largely when the intestine is emptied above by the artificial anus, because putrefaction of the intestinal contents is only just beginning at this stage of digestion, or is wholly absent, and the amount of putrefactive substances capable of being absorbed is exceedingly small. Repeated observations have been made since the Baumann experiment, and have fully established the correctness of his view of the origin of the ethereal sulphates.

It would be interesting to make some studies to determine whether there are simultaneous variations in the excretion of ethereal sulphates and in the number of bacteria in the fæces, especially the common colon bacilli. I do not know that such studies have yet been made.

We are liable to meet with an increase in the ethereal sulphates of the urine whenever any of the aromatic bodies already referred to as arising in the intestine, namely, indol, skatol, phenol, or kresol, is distinctly increased. I say we are liable to meet with such an increase under these circumstances, for it may happen that when one of the ordinarily present aromatic bodies is considerably increased, the others are present in quantities below the average amount. At least it is in this way that I explain to myself the increase in indican of the urine, derived from indol, which we sometimes find in the urine without any

corresponding increase in the total amount of the ethereal sulphates of the urine.

Since the ethereal sulphates are derived from various aromatic substances produced during the decomposition of proteids in the intestine, the amount of these sulphates must be influenced by the quantity of the individual aromatic products thus formed. Now it is certain that these different products are formed as the result of different conditions of bacterial activity in the small intestine and colon. We are not by any means well informed as to the nature of these different conditions, and, therefore, it is not possible to give a really scientific and fundamental explanation of the significance of the increase of the ethereal sulphates. What we know of the conditions attending the excessive production of the ethereal sulphates has to do with more or less carefully observed clinical conditions, and not with well studied chemical and bacterial processes. Still it is of interest to know that in clinical states pointing to intestinal indigestion the ethereal sulphates are increased. Although positive proof is lacking, it is likely that the cases of intestinal indigestion which run a chronic course are dependent on chronic catarrhal enteritis. In the acute cases of intestinal indigestion there is probably an acute catarrhal enteritis of slight or considerable severity, but that histological changes in the mucous membrane of the intestine are necessary before there can be an excessive degree of putrefaction cannot be maintained. A very large meal of meat is apt to be followed by an absolute and relative increase in the ethereal sulphates. The increase of sulphates observed in the course of diverse clinical conditions, such as migraine, epilepsy, diabetes, jaundice, gastric ulcer, &c., can with much likelihood be referred to underlying or associated catarrhal disturbances in the small or large intestine, or to constipation.

It often happens that constipation is associated with an excess of ethereal sulphates in the urine, and it seems reasonable to believe that a delay in the emptying of the intestinal contents is one of the conditions most favourable to the multiplication of bacteria engaged in effecting the putrefactive decomposition of proteids. There are, however, instances in which transient constipation appears not to increase distinctly the outgo of the aromatic sulphates by the urine.

That stasis of the contents of the intestine is peculiarly

favourable to the development of putrefactive bacteria and their products is shown by the circumstance that occlusion of the intestine, either large or small, is followed regularly by a great increase in the elimination of aromatic sulphates.

This increase has been repeatedly noted both in the human subject and in experimental observations upon dogs. The excessive output of the sulphates lasts as long as the occlusion continues, and is often found where there is only partial occlusion of the large or small intestine. With the relief of the obstruction there is a rapid return to normal conditions of putrefaction. The evidences of putrefaction are less pronounced in occlusions of the upper part of the small intestine than in the lower portion or in the colon.

It is important to recognise that there are two sources for the ethereal sulphates of the urine quite unconnected with the occurrence of putrefaction in the intestine. The ethereal sulphates may be increased in consequence of putrefaction in other parts, especially where there is extensive suppuration without free drainage. Such an increase has been observed in abscesses in various parts, in tuberculous cavities of the lung, and in cases of empyema. Of course the sulphates in such instances as these are derived from the decomposition of proteid substances.

The second source of ethereal sulphates, external to intestinal putrefaction, is found in the use of certain drugs of an aromatic nature. Thus there is a marked increase in the ethereal sulphates after the ordinary doses of benzosol, salol, salophen, creosote, and other aromatic substances. It is obvious that it will not do to overlook this source of ethereal bodies in the urine. You must positively exclude the use of these much-employed drugs before you can draw any inference in regard to ethereal sulphates derived from intestinal putrefaction.

From the standpoint of the physician the most important question about the aromatic substances formed in the intestine and excreted as ethereal sulphates is whether these substances have any toxic action upon the organism. As you can readily see from what I have already told you, this question can only be answered satisfactorily where we are in possession of a knowledge of the physiological properties of the individual aromatic substances split off from the proteid molecule in the course of intestinal putrefaction. In a few minutes I will undertake to tell you

something about the properties of two of these bodies, phenol and indol, which have been more thoroughly studied than the others. In the meantime it may be said that the formation of unusually large amounts of the aromatic derivatives in the intestine must always be regarded as injurious to the organism, although there is as yet no evidence that serious injury to the cell structures of the human body is ever brought about through the agency of phenol, kresol, indol, or skatol. On the other hand I consider that such evidence as we possess in reference to this subject indicates that the long-continued activity of some of these substances in excess is capable of bringing about various derangements in the functions of the central nervous system.

In speaking to you of the chemical defences of the organism against disease I told you something about various synthetic activities of cells which protect the nervous system from the action of toxic substances by combining these substances in such ways as to render them less harmful. Among such synthetic processes with a detoxicating action are the various combinations of sulphuric acid with the aromatic bodies of which we have been speaking. We have therefore to regard the ethereal sulphates of the urine, not as poisonous bodies, but as combinations in which the original aromatic bodies, like indol and phenol, have been largely deprived of their toxic properties.

One other point remains to be noted before we take up the consideration of individual aromatic bodies. The supply of sulphuric acid is by no means inexhaustible. Hence it is that when the aromatic bodies which undergo pairing with sulphuric acid are abundant, the sulphuric acid in the preformed sulphates is correspondingly decreased. The aromatic substances are sometimes so abundant that all the sulphuric acid available is used in the pairing process, with the result that the preformed sulphates disappear wholly from the urine. We see this well illustrated by cases of carbolic acid poisoning. Here the phenol takes all the available sulphuric acid to make salts of phenol-sulphuric acid in which the sulphuric acid does not react with barium chloride. Hence when we add barium chloride to the urine from such a patient there is no precipitation of barium sulphate, because there is no sulphuric acid present as preformed sulphate. This behaviour of the urine is of course in distinct contrast to the behaviour of normal urine, in which

the addition of barium chloride causes the prompt separation of barium sulphate.

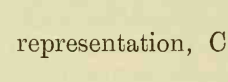
It would be an error to suppose that the resources of the body for the neutralisation of aromatic substances are exhausted when the available sulphuric acid has been united to such substances. When this happens, as may occasionally be the case in disease, or as frequently happens under the administration of drugs of the aromatic series, the aromatic substances unite with glycuronic acid, and are excreted as glycuronates. This glycuronic acid, to which I shall refer again in speaking of diabetes, is derived from glucose, and is only found in the urine in appreciable quantity when it has been spared from combustion by pairing with aromatic substances. The relationship of glycuronic acid to glucose is suggested by its chemical constitution, which is expressed by the following formula :—

$$CHO.(CH.OH)_4COOH = (C_6H_{10}O_7).$$

We may now consider some of the properties of the individual products of intestinal putrefaction.

Such observations as have been made upon the phenol of the urine include for the most part the closely related kresol. The quantity of these bodies found in the normal urine is very small. In conditions of disease there is sometimes a considerable increase. Thus a distinct increase has been noted in obstruction of the intestine, in some cases of peritonitis, in anæmias, in diabetes, in typhoid fever, and in some so-called cachexias. I have found a very great increase in a case of carcinoma of the head of the pancreas, attended with other evidences of excessive intestinal putrefaction. In general it may be said that whenever the ethereal sulphates are much increased an excess in the phenol of the urine can be detected. There is, however, some reason to think that the phenol output is at times increased out of proportion to the output of other putrefactive substances. We do not know anything definite about the conditions under which the bacteria of the intestine produce phenol or kresol rather than indol or skatol or other putrefactive materials. On this subject we have a great deal to learn. At the present time we do not really know even the clinical states that are regularly attended by an increase in phenol. Since no special diagnostic meaning beyond evidence of putrefaction can at present be attached to the presence of phenol in the

urine I shall not touch further on this subject, but shall tell you something about the excessive formation of indol, a product in reference to which we are somewhat better informed.

Indol is a volatile aromatic substance of fæcal odour which crystallises in white glancing crystals, and is only slightly soluble in water. In the intestine it is derived from the putrefaction of proteids, and possibly to a slight extent from the decomposition of proteids under the influence of the pancreatic ferment known as trypsin. The formula C_8H_7N represents indol, but does not show the linking of the nitrogen atom contained in the molecule. This is seen in the following representation,  , which also indicates the aromatic nucleus of the product. Indol, like phenol, is probably derived from the decomposition of the more complex body tyrosin ($C_9H_{11}NO_3$), which, as I explained in discussing the proteids, is one of the cleavage products of this class of food-stuffs.

When indol is formed in the intestine as the result of putrefaction, or is introduced experimentally, absorption rapidly takes place. The indol carried by the portal blood to the liver is there held in loose combination apparently with the living protoplasm of the liver cells, a combination which is soon replaced by a union with sulphuric acid. It is believed that the oxidation of indol to indoxyl occurs before this union with sulphuric acid. The indoxyl sulphuric acid thus found in the liver cells, and sometimes in other cells also, probably exists as a potassium salt—indoxyl sulphate of potassium ($C_8H_6NOSO_3K$). This compound finds its way into the blood in small amounts, and is promptly excreted by the kidneys. It is known as indican. It was called indican in the mistaken belief that it is identical with the indican of plants, and the name has clung to it.

When the indican of the urine undergoes oxidation indigo blue is formed and gives to the urine a characteristic blue colour. This indigo blue is not indican, but is evidence of the pre-existence of indican in the urine. The reaction by which the change into indigo blue occurs is as follows:—

$$\underset{\text{Indoxyl-sulphate of potassium.}}{2C_8H_6NKSO_4} + O_2 = \underset{\text{Indigo blue.}}{C_{16}H_{10}N_2O_2} + \underset{\text{Acid potassium sulphate.}}{2HKSO_4}$$

The test for the detection of indican in the urine is so easily and quickly carried out that it is coming to be extensively used by practitioners, and there is no excuse for a failure on your part to learn to recognise whether the urine contains a normal or an excessive amount of indoxyl-potassium sulphate.

But how are we to form an opinion as to whether the indican reaction is more pronounced than normal? I have to own that we cannot always reach a conclusion on this point, for there is no arbitrary criterion which can be safely applied in all cases. It seems to me necessary in every case to take into consideration whether the subject you are studying is robust or feeble, for a slight reaction for indican in a vigorous individual may have no practical significance, whereas a reaction of the same intensity in a feeble individual may be indication of the existence of a harmful process. The occasional appearance of a slight indican reaction in the urine of an adult has no pathological significance, but the persistent occurrence of a moderately strong reaction is abnormal and objectionable. It is indeed true that there may be none of the obvious signs of intestinal disorder; but if my experience does not mislead me in reference to this point, the subject whose urine gives a persistently marked reaction for indican sooner or later shows clinical evidences of impaired intestinal digestion. *A fortiori* this is true of persons in whom there is a very strong reaction constantly or most of the time. It is, however, very important for you to recognise a fact which many physicians overlook—namely, that the local evidences of intestinal disturbances, such as flatulence, irregular and foul stools, &c., may be much less important than the remote evidences of excessive intestinal putrefaction, such as loss in weight and strength, and a variety of symptoms of nervous disorder which are usually classed as neurasthenic in character. I should not omit to mention to you that the urine of young children is normally free from indican. Senator long ago noticed that in newly born children the urine contains no indican, and I can confirm this observation as being true of the first months of life. My experience indicates that in children under five years of age anything more than a trace of indican is pathological if it be persistent.

Still another point of importance in forming a judgment as to whether there is excessive putrefaction of proteids in

the intestine must be mentioned. You will find it helpful to make numerous observations on the urine (both on separate samples and on the mixed amount for the twenty-four hours) extending over a long period of time. If you find that the indican reaction grows less as the symptoms improve, and it regularly increases whenever the patient shows the recurrence of a certain train of derangements, the likelihood of a causal relationship is much increased. On the other hand, if the indican and symptoms vary independently and not concomitantly, you will have to abandon the view that the indol formation in the intestine is closely connected with the disturbances which you are treating.

The clinical conditions under which one is apt to find a considerable increase of indican are numerous and not easy to group satisfactorily. In general, it may be said that the indican of the urine is commonly increased in all conditions that increase the total excretion of ethereal sulphates. But, as I have already intimated, there are numerous exceptions to this rule.

Perhaps it will help you if I enumerate the clinical states in which we most frequently find a strong indican reaction. The strongest reactions are obtained in cases of intestinal obstruction, and are regularly present in obstructions below the middle of the jejunum. In most instances of even partial obstruction the indoxyl-potassium sulphate is in excess. In duodenal obstructions and obstructions of the pylorus I have usually found an excess of indican. Many of these high obstructions occasion a state of partial starvation, and, as I shall point out in speaking of starvation, the local conditions that exist in this state are peculiarly favourable to intestinal putrefaction. Ordinary constipation does not necessarily occasion a strong indican reaction; when it does the increase is probably connected with associated catarrhal disturbances in the intestine; for such disturbances are a common cause of excessive decomposition of proteids in the intestine. The excess of indican noted in some cases of epilepsy (especially near the seizure) is usually associated with such catarrhal disorders. The same is true, I think, of muscular rheumatism.

Some writers believe that any condition in which the free hydrochloric acid of the gastric juice is diminished or absent is regularly associated with a marked reaction for indican, due to the absence of the antiputrefactive influence of the

gastric juice. It is certainly true that this is one important cause of excessive putrefaction in the intestine, and I think that the indicanuria noted so often in chronic nephritis, in anæmias, in rheumatoid arthritis, in diabetes, in jaundice, and in most instances of chronic gastritis, is due in part to the diminished secretion of free hydrochloric acid. The relationship, however, is not a constant one, for there are cases of achlorhydria where there is no indican, and cases of hyperchlorhydria with an excess of indican. Intestinal disturbances attended with impaired secretion of bile or pancreatic juice (or both) are usually associated with an increase of indican. I suspect that the increase of indican noted in persons who masturbate or commit sexual excesses is connected with diminution of the intestinal secretions.

One cause of indicanuria, of which the importance has been overestimated, is suppurative disease, as where abscesses become infected with putrefactive bacteria. Another condition in which an increase of indican has been considered characteristic is tuberculosis. Some observers even go so far as to regard the indicanuria of childhood as highly suggestive of tuberculosis. I look on this view as erroneous, and believe that the reason why tuberculous children have indican in their urine with such frequency is that they are very liable to have digestive derangements.

If now you were to ask me to enumerate the most frequent pathological causes of a decided excess of indican, I should reply by saying that these causes are chiefly three: (*a*) diminished secretion of free hydrochloric acid; (*b*) diminished secretion of the intestinal digestive juices; and (*c*) the excessive use of proteid food, specially meat. The first operates partly by withdrawal of the antiputrefactive action of the gastric juices, partly by impaired digestion of proteid which exposes these foods to the action of putrefactive bacteria when they reach the intestine. The diminished secretion of the intestinal digestive juices, bile, and pancreatic juice acts, I imagine, through exposure of the undigested proteid to the action of micro-organisms. In many instances the impaired gastric and intestinal secretions are associated. Of course catarrhal inflammation of the stomach and of the small intestine is the commonest and most important cause of these diminished secretory activities. The influence of meat is accounted for by the readiness with which meat yields indol during putrefaction.

Probably you will now ask whether we know anything about the putrefactive process itself—the process of decomposition by which indol is formed in such quantities as to increase the indican of the urine. The one important thing to remember in this connection is that the chief bacterial inhabitant of the intestine of permanent and obligatory character is also an energetic producer of indol under favourable conditions. Of course you are aware that the colon bacillus group includes many varieties, some of which are only weak indol producers. It is also true that other species of bacteria are indol makers, and may contribute to the formation of the indol made in the human intestine. Nevertheless I believe that the indol made in the human gut is very largely the product of the colon bacillus acting on proteid material. As I showed several years ago, the direct injection into the intestine of a pure culture of colon bacilli, in large numbers and in a medium free from indol, is followed by a regular and great increase of the indican of the urine.

The indol production of the colon bacilli is influenced by a number of conditions. First, the bacteria themselves may grow either more active or less active in their ability to make indol. Secondly, when both proteids and carbohydrates are present the colon bacillus decomposes especially the latter, and thus little or no indol is made until the supply of carbohydrate runs low or is exhausted. Perhaps this is one reason why milk, with its large content of lactose, is so ununfavourable to the development of indol. Probably, also, there is a difference in the readiness with which different proteids yield the tyrosin from which indol springs. On this point we are not yet satisfactorily informed. The mere presence of the lactic acid bacillus in very large numbers in the intestine appears to be a check on the indol production of the colon bacilli, notwithstanding the organisms of this group are, with few exceptions, capable of yielding indol in small amounts if allowed to grow sufficiently long on proteid media.

A question of the first interest in connection with indol is whether it possesses any toxic properties in virtue of which it is capable of creating disturbances in the human subject. Not long ago I gave some attention to this subject and went so far as to induce persons to take considerable doses of the pure crystals of indol for the purpose of observing

any pathological effects that might result. I found that the susceptibility to its influence varied considerably in different individuals. The conclusions I reached are that indol is only moderately toxic to man; that small doses are liable to produce frontal headache and a condition of irritability and restlessness; that larger doses may be the cause of diarrhœa without other symptoms, or may induce a condition of marked irritability, insomnia, and mental confusion; and, finally, that the continual absorption of enough indol to yield a constant strong reaction for indican in the urine is capable of inducing neurasthenic symptoms.

In a more recent study of indol and phenol I have made some more observations on the manner in which the cells of the body—especially the cells of the liver, but also those of the muscles and of the intestinal mucous membrane—screen the central nervous system from the toxic action of indol. I cannot give you the details of my experiments, but refer those of you who have an interest in the subject to my original papers.

While I recognise that other products of putrefaction than indol may possibly have even more important chronic effects upon the organism, I am confident that indol absorption contributes in no unimportant way to the production of chronic disorders of nervous functions.

I have often observed that urines containing a large amount of ethereal sulphates decompose less rapidly than most other urines, and am disposed to attribute this greater resistance to bacteria to the presence of aromatic bodies. I do not, however, feel sure that this is the correct explanation. I have also noticed that persons with large amounts of indican in the urine are apt to pass their urine too often. Possibly this is owing to the associated fermentative disorders that are so common—disorders which we discussed last week. But it is also possible that the presence of large amounts of ethereal sulphates acts as a local irritant to the bladder. I think the point worthy of investigation.

I do not consider it possible at the present time to form a final judgment in reference to the precise part played by indol as a toxic substance. This is because our knowledge of the putrefactive substances in their relation to disease is distinctly 'patchy.' We happen to know something about indol because we have a striking and easily applied test for indican; but other substances less easily followed in the

organism may possess equal or greater importance. Some of these products of putrefaction cannot be passed by without notice, although our knowledge of their effects on the body in pathological states is by no means complete.

The ordinary products of proteid decomposition under the action of bacteria belong in part to the aromatic series, in part to the fatty series of compounds. The aromatic bodies indol, skatol, parakresol, and phenol have been sufficiently discussed for our present purpose. The compounds of the fatty acid series are for the most part the same as those which we have already considered in speaking of the products of fermentative activity of carbohydrates, and include the various volatile fatty acids—formic, acetic, propionic, &c. The more important gases that arise from proteids under the influence of putrefactive bacteria are carbon dioxide (CO_2), hydrogen (H), marsh gas (CH_4), ethyl mercaptan (C_2H_5S, a sulphur alcohol), and sulphuretted hydrogen (H_2S). Besides these products there are certain compounds representing a union of aliphatic and aromatic radicals. Thus we have phenyl-propionic acid ($C_6H_5CH_2.CH_2.COOH$) and phenyl-acetic acid ($C_6H_5CH_2.COOH$), in each of which the aromatic radical (C_6H_5) is united to a fatty acid radical. Furthermore, there arise the corresponding aromatic hydroxy-acids, para-oxy-phenyl-acetic acid ($C_6H_4.(OH)CH_2.COOH$) and para-oxy-phenyl-propionic acid ($C_6H_4(OH)CH_2.CH.COOH$), in which one of the hydrogen atoms is replaced by a hydroxyl (OH) group. Please understand that these various aromatic derivatives, like phenol, indol, &c., come only from the decomposition of tyrosin, and that nitrogenous substances which, like gelatin, yield no tyrosin are unable to yield aromatic oxyacids.

The aromatic hydroxyacids (para-oxy-phenyl acetic acid and para-oxy-phenyl-propionic) find their way into the urine, and their presence is easily recognised by simple procedure. These products of putrefaction are probably increased in most cases where the ethereal sulphates of the urine are present in excess. It may be their presence in larger amount than usual is an evidence of some peculiar conditions of putrefaction, but as to the nature of these peculiarities we are at present quite in the dark.

A product of proteid intestinal decomposition which has received little attention is benzoic acid ($C_6H_5.COOH$). It s known that benzoic acid unites in the organism with

glycocoll (amido-acetic acid) ($CH_2.NH_2.COOH$) to form hippuric acid ($CH_2<^{NH.CO.C_6H_5}_{COOH}$) or benzoyl glycocoll. Now hippuric acid occurs in normal human urine in considerable amount, and I think there is some evidence that in digestive derangements the quantity excreted by the urine may be increased. A part of the benzoic acid required to form hippuric acid is derived from the vegetable food, but, according to Baumann, it is also a product of intestinal putrefaction.

I have told you that proteid putrefaction is commonly associated with the formation of compounds containing sulphur, among which are sulphuretted hydrogen and methyl mercaptan. Both sulphuretted hydrogen and mercaptans are normally produced in small amount in the large intestine, and in conditions of excessive putrefaction the sulphur of the proteids may perhaps yield enough of these sulphur compounds to result in harmful effects upon the organism. In the case of sulphuretted hydrogen it was formerly taught that the absorption of this gas in considerable amount is capable of inducing a train of nervous symptoms comparable to the effects observed when there has been absorption after inhalation effects many times seen in workmen engaged in cleaning sewers and cesspools. These symptoms consist in headache, dulness, giddiness, and prostration. They are said to be associated with the appearance of sulphuretted hydrogen in the urine—an occurrence to which the name hydrothionuria has been given.

After the publication of Senator's classical description of an instance of hydrothionuria of intestinal origin and associated with marked nervous symptoms, it appeared as if a number of nervous symptoms might be attributable to poisoning by sulphuretted hydrogen absorbed in the course of digestive disturbances. Modern investigation has, however, failed to confirm the view that sulphuretted hydrogen plays an appreciable part in the production of symptoms of disease. The question is one, however, which I regard as being far from settled. It has been repeatedly shown that sulphuretted hydrogen acts injuriously on the nervous system, whether it enters the body by the lungs or by the digestive tract. One can easily convince himself of the reality of these toxic properties by allowing a current of

the gas to enter the rectum of a dog. A surprisingly small quantity suffices to induce fatal coma, perhaps attended by convulsions. There is certainly no good reason for supposing that sulphuretted hydrogen derived from intestinal putrefaction is often responsible for the onset of acute or severe disorders of nervous function. On the other hand, we are not in a position to deny that the long-continued absorption of small quantities of the gas from day to day is without harmful effects. It is indeed difficult to understand how a gas so toxic to the nervous system can be absorbed even in moderate quantities from the digestive tract without bringing about derangements. And I may take this occasion to say that it seems to me pathologists do not yet pay enough attention to the prolonged and cumulative effects of pathological conditions which, when they act only for a short time, induce no pronounced disorders of function or structure. One would hardly be led to suppose that the removal of fat from the food induces pathological conditions, for no structural changes can be detected during the early months of such privation. But after the lapse of many months we may be confronted with a change so marked as the serous atrophy of adipose tissues. Similarly the effects of moderate indol absorption may be hardly discernible for many days, while more prolonged absorption leads to distinctly marked nervous symptoms. I do not mean to state that the case is the same with the absorption of sulphuretted hydrogen. I wish, however, to say that it may be the case for aught we know to the contrary.

We know something about the conditions under which sulphuretted hydrogen arises in the course of putrefaction in the digestive tract, and I cannot pass on without alluding to them.

In the first place it is well established that a majority of the aërobic bacteria and most or all of the known anaërobic bacteria of the digestive tract are capable of producing sulphuretted hydrogen from proteids under favourable conditions. Among the conditions favourable to such gas production are a low content of hydrochloric acid in the gastric juice and the absence of oxygen. A high content of free hydrochloric acid is unfavourable to the development of all bacteria in the stomach, and the amount ordinarily present is sufficient to prevent any formation of sulphuretted

hydrogen. This is clearly shown by the recent careful study of Dauber. As might be expected, it is in cases of dilatation of the stomach, with great retardation in the expression of the contents, that we are most likely to find a development of sulphuretted hydrogen within the stomach.

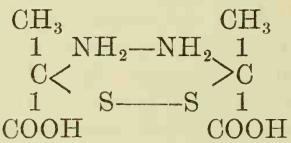
I just now told you that the absence of oxygen is a condition favourable to the production of sulphuretted hydrogen by bacteria. Perhaps I can make it clear to you why this is the case. You know that the bacteria of the gastro-enteric tract produce a considerable amount of free hydrogen in the nascent state. This hydrogen unites very readily with oxygen to form water. It thus exerts a reducing action on compounds or solutions containing oxygen, and this reducing power of the bacteria is one of the most characteristic processes pertaining to the intestinal flora. Now so long as oxygen is present which can unite with the nascent hydrogen any sulphur present in sulphites or sulphates remains in this form. When, however, the available oxygen has been united to hydrogen, the continued formation of nascent hydrogen leads to the union of this hydrogen with sulphur, an element which, as you know, has many points of resemblance to oxygen. Thus the sulphites and hyposulphites, and, in some instances, even the sulphates, suffer a reduction in which they are deprived of their sulphur, with the resulting formation of sulphuretted hydrogen. The sulphur of these inorganic compounds is, however, not the only source of sulphuretted hydrogen. Many bacteria appear to have the power not only of producing hydrogen gas, but of splitting sulphur from the proteid molecule. Where this double action occurs in the absence of oxygen the formation of sulphuretted hydrogen is inevitable.

It should now be clear to you why the absence of oxygen favours the formation of sulphuretted hydrogen, and why the anaërobic bacteria of the intestine are such regular producers of the gas. You can also understand why very little of the gas is formed in the upper parts of the intestine in comparison with the lower portions.

Some patients with excessive intestinal putrefaction have flatulent discharges from the rectum which smell of sulphuretted hydrogen. The use of sulphur as a laxative somewhat increases the amount of the gas in normal people, but has no appreciable effect in the production of toxic symptoms.

I have now told you something of the more common types of putrefaction in the intestine, but before quitting the subject it is proper that I should bring to your notice some exceptional kinds of putrefaction which have a certain clinical interest. One of these types of putrefaction is associated with the appearance of cystin in the urine, giving rise to cystinuria; another has to do with the condition known as alkaptonuria; and still another has reference to the production of the basic bodies, neurin and cholin, within the intestinal tract.

The term 'cystinuria' relates to the appearance of the substance cystin in the urine. Cystin ($C_6H_{12}N_2S_2O_4$) is the disulphide of di-amido-ethidenelactic acid, and its molecule is represented as follows:—



Being slightly soluble in the urine, cystin readily separates, and is recognised as a sediment consisting of hexagonal glancing crystals. These crystals are freely soluble in ammonia and in hydrochloric acid, but are insoluble in water, alcohol, ether, and acetic acid. The amount of cystin in the urine sometimes reaches half a gram or a gram in the twenty-four hours; usually the quantity is less, and in some cases cystin is temporarily absent.

Cystinuria cannot be regarded as having a great clinical interest, because it is commonly unassociated with definite symptoms, and may indeed be well developed in persons apparently in good health. Still, we cannot overlook the fact that cystinuria occurs, as a rule, in persons with the clinical indications of disordered digestion, not infrequently associated with anæmia. In two cases which I had under observation the ethereal sulphates were increased. Moreover, cystinuria has in some cases a certain importance for the surgeon, since calculi are occasionally formed which consist largely of cystin.

To the student of chemical pathology the problems connected with the phenomena of cystinuria are of much greater interest, because their explanation is closely bound

up with a number of more or less obscure but important biological processes.

Perhaps the most striking fact at present known to us in relation to the pathology of cystinuria is the almost regular association of this condition with the presence in the excreta of putrefactive basic bodies or ptomaines belonging to the class of diamines. The diamines are, you remember, bodies in which two amine (NH_2) groups are united to a diatomic alcohol radical of the olefine series of hydrocarbons. The diamines of greatest interest in connection with cystinuria are tetra-methylen-diamin and penta-methyl-diamin. The constitution of tetra-methylen-diamin or putrescin is as follows :—

$$\begin{array}{l} CH_2—CH_2—NH_2 \\ \quad | \\ CH_2—CH_2—NH_2 \end{array}$$

The constitution of penta-methylen-diamin or cadaverin is represented thus :—

$$\begin{array}{l} CH_2—CH_2—NH_2 \\ \quad | \\ CH_2 \\ \quad | \\ CH_2—CH_2—NH_2 \end{array}$$

The cases of cystinuria that have been carefully studied are still too few to enable us to make sweeping generalisations in reference to the occurrence of these diamines in the urine and fæces. Nevertheless, there is no doubt that by careful methods of study these bodies are generally found in the excreta of patients with cystinuria, putrescin commonly preponderating in the fæces, cadaverin in the urine. Although skilled chemists have failed in a few instances to find diamines in the urine and fæces of cystinuric patients, it is not by any means clear that this failure was not referable to imperfections in the process originally employed for their separation. I do not, therefore, think we are justified at present in assuming that there are any cases of cystinuria unaccompanied by the appearance of diamines in the urine or fæces throughout the duration of the condition. In an instance recently reported by Cammidge and Garrod the urine failed to show the presence of diamines during so considerable a period as twenty-three successive days.

At other times, however, cadaverin was found. What interpretation are we to place on this intimate, if not regular, association of cystinuria with the excretion of putrescin and cadaverin? This is a question to which a wholly satisfactory answer cannot be given. We know that these diamines are products of bacterial action upon proteids, and the only tenable view as to their occurrence in the urine and fæces is that they have their origin in putrefactive processes in the intestine—processes the conditions of which are unknown to us. The idea at once suggests itself that the cystin of the urine is similarly of bacterial origin. This was, in fact, the view to which Baumann, the discoverer of diamines in cystinuria, was inclined.

There is, however, excellent reason to believe that cystin is an intermediate product of normal metabolism which is ordinarily broken up with oxidation of the greater part of its sulphur to sulphuric acid. The formation of cystin is apparently preceded in the course of normal metabolism by cysteïn. This cysteïn is to be regarded as a lactic acid, $CH_3.CH.(OH)COOH$, in which one H is replaced by NH_2 and the OH by SH, thus :—$CH_3.C\begin{pmatrix}SH\\NH_2\end{pmatrix}.COOH$. Cysteïn is therefore regarded as an amido-thiolactic acid.

The action of atmospheric oxygen is capable of converting cysteïn into cystin as shown in the representation of the molecules

$$2CH_3—\underset{\underset{SH}{|}}{\overset{\overset{NH_2}{|}}{C}}—COOH + 2O = \begin{matrix}CH_3—CSNH_2—COOH\\ \quad\quad\quad\quad\quad\quad\quad\quad |\\ CH_3—CSNH_2—COOH\end{matrix}$$

Cysteïn. Cystin.

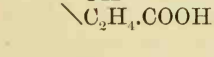
In cystinuria it is evident that the cystin is not normally split and oxidised, just as in diabetes the sugar furnished by the metabolic activities of the cells is neither split nor burned. It may be that it is the diamines which act on the cells in such a way that cystin escapes the normal cleavage and oxidation. Udransky and Baumann, however, failed to produce cystinuria in dogs by the administration of diamines. It is, on the whole, not unlikely that both the diamines formed by putrefaction in the intestine and the cystin formed

in the course of metabolism are expressions of an obscure form of putrefactive decomposition in the intestine. Please remember, however, that there is no evidence that cystin itself is a product of putrefaction.

The fæces from a patient with cystinuria were introduced directly into the small intestine of one of my dogs. The animal developed persistent diarrhœa, but the urine failed to show the presence of cystin.

I desire now to allude briefly to the condition of intestinal putrefaction that results in alkaptonuria. Alkaptonuria is the name given to a peculiar pathological state in which the urine on exposure to the air or on the addition of alkalis grows dark green or brown near the surface, and may ultimately become almost black. The change is due to the presence of uroleucic or homogentisic acid, and is the consequence of an oxidative process. The most likely view is that homogentisic acid, and probably also uroleucic acid, is derived from tyrosin. The chemical relationships between uroleucic acid, homogentisic acid, and tyrosin are partially indicated by the following constitutional formulæ :—

Uroleucic or tri-oxy-phenyl-propionic acid



Homogentisic or dioxy-phenyl-acetic acid

Tyrosin or amido-oxy-phenyl-acetic acid

That homogentisic acid is derived from tyrosin—one of the products of putrefaction—is rendered likely by the fact that tyrosin administered by the mouth causes the presence of considerable homogentisic acid in the urine. It has further been found that a portion of the homogentisic acid taken by mouth reappears in the urine.

The decomposition of tyrosin, with a yield of homogentisic acid, may perhaps arise in consequence of unusual putrefactive conditions. Some writers have indeed urged that the homogentisic acid has its origin in metabolic derangements, but the probabilities appear opposed to this view.

The term 'alkaptonuria' was applied to this condition to which I am referring in the belief that it depends on a body to which the name 'alkapton' had been given. This

substance has, however, been shown not to be a definite compound, and the darkening of the urine is apparently sometimes due to homogentisic acid, or, less frequently, to uroleucic acid, or to pyrocatechin ($C_2H_4(OH)_2$).

Alkaptonuria is an uncommon occurrence, and has at present little clinical significance, as it is not regularly associated with any definite symptoms of disease. Slight digestive derangements appear to be common among the subjects of alkaptonuria, and the ethereal sulphates are often somewhat increased. The urine of alkaptonuria reduces Fehling's solution, and unless you exercise some care the presence of sugar may be suspected. But the alkapton urine differs from sugar-containing urine in that it neither ferments nor reduces alkaline bismuth solutions. It is also optically inactive.

You will recall that I spoke to you about the conversion in the organism of phenol or carbolic acid ($C_6H_5(OH)$) into phenol-sulphuric acid, and its excretion in the urine as an ethereal sulphate. When large quantities of carbolic acid have been taken into the body a certain portion of the phenol is further oxidised into hydroquinone ($C_6H_4(OH)_2$) which is *p*-dioxybenzol. This hydroquinone probably passes into the urine as an ethereal sulphate. On exposure of the urine to the air it undergoes decomposition into an aromatic substance, which gives the upper portion of the urine a dark colour very similar to that observed in alkaptonuria. The condition is sometimes known as carboluria. I mention it merely because of its resemblance to alkaptonuria.

The last products of intestinal putrefaction which I shall mention are the basic substances neurin and cholin.

The substance cholin has the formula

$$(CH_3)_3{\equiv}N\begin{matrix}\diagup OH\\ \diagdown CH_2CH_2OH\end{matrix}$$

and is thus to be regarded as trimethyl-oxyethyl-ammonium hydrate. It appears to be identical with a substance in certain mushrooms which is known as amanitin. The body neurin has the formula $(CH_3)_3{\equiv}N\begin{matrix}\diagup OH\\ \diagdown CH = CH_2\end{matrix}$, and is known as trimethyl-vinyl ammonium hydrate. In weak watery solutions cholin is capable of being transformed into

neurin, and this transformation is one which may be facilitated by the action of micro-organisms.

Now it is important for you to understand that the widely distributed lecithins of the body are constituted through a union of fatty acids and glycero-phosphoric acid with the base cholin. Lecithins are present in very many articles of food, and in some, such as the yolks of eggs, the eggs of fishes, and the substance of the brain, they are abundant. There is thus the possibility that the decomposition in the intestine of food-stuffs containing lecithin in considerable quantity may yield cholin in sufficient amount to be of pathological significance. The pathological importance of cholin as such is small, for it is an almost inert body. But, as I have just mentioned to you, cholin is capable of conversion into neurin. Neurin, unlike cholin, is highly toxic. It causes cardiac depression, lowering of arterial tension, and great irritation of the intestinal mucous membrane, which causes an increased peristalsis and frequent evacuations. These toxic effects are much like those induced by muscarin.

The recent experimental work of Nesbitt shows that if intestinal obstruction be produced in dogs that have been fed on lecithin-containing foods like the yolks of eggs, neurin and cholin can be subsequently found in the intestinal contents. It has been suggested that in human intestinal obstruction pain and excessive peristalsis, together with the prostration and collapse, are due in part to neurin. Further investigation is essential to determine whether this is really the case. It would also be of interest to know whether the toxic symptoms noted in some persons after the eating of eggs are due to the action of cholin.

At present we know nothing definite of the character of the bacterial conditions in the intestine which favour the production of cholin from lecithin and the conversion of cholin into neurin.

I hope that this sketch of the more important fermentative and putrefactive processes and products, incomplete though it is, will be of some service in clarifying your ideas in regard to what goes on in the digestive tract in conditions of disease. It is desirable to recall the distinction already mentioned between (*a*) cases of gastric-enteric disorder in which there is an absorption of deleterious bacterial products, but in which the bacteria themselves do not pass

through the intestinal walls into the circulation; and (*b*) cases in which both the bacteria and their products pass through the intestinal epithelium into the general circulation. To the latter class of cases belong many instances of severe acute enteritis and entero-colitis and typhoid fever. These are really instances of septicæmia of gastro-enteric origin. To the former class of cases belong the ordinary intoxications of gastro-enteric origin, of which we see so many in practice. This group of cases includes the so-called auto-intoxications of intestinal origin. We have to distinguish between the gastro-enteric intoxications which arise from the excessive putrefaction of ordinary food-stuffs, and those which have their origin in food ingested in a state of decomposition. In the former case only the ordinary saprophytic bacteria are introduced with the food, and the putrefactive products are mainly the action of the colon bacilli or allied organisms. In the latter instance the intoxication is dependent on the introduction of specific poisons made by specific micro-organisms. We see examples of such intoxication in severe cases from poisoning from milk, in poisoning from cheese (tyro-toxicon poisoning), and in the poisoning from meat known as *botulism*. In the case of botulism we have to deal with a highly characteristic symptom-complex, consisting mainly of disturbances of secretion, symmetrical motor palsies, due probably to lesions of the central nervous system, and the symptoms of acute gastro-enteritis. This condition, which often terminates fatally, has been shown by the admirable work of Van Ermengen to depend on the action of a specific toxin formed by an anaërobic bacillus, and subsequent investigations have shown that by means of this toxin it is possible to induce the formation of an immunising antitoxic serum. The same poison is probably the cause of the toxic symptoms observed in certain cases of intoxication after the use of ham, sausage, fish, and other infected foods.

Many cases of botulism, of poisoning by infected milk, of poisoning from cheese, &c., are recognisable by the clinical history and epidemic or endemic occurrence. It is not possible, however, to separate sharply in clinical practice the group of intoxications due to infected food, and the group of intoxications arising from poison developed in the gastro-enteric tract. Neither are we able at present always to separate the intoxications due to the absorption of

bacterial products from those in which there is also an entry of pathological bacteria into the circulation. Modern studies indicate that a septicæmia of gastro-enteric origin is by no means rare among the severe diarrhœal diseases of children, where such a septicæmia was formerly unsuspected. At present we are unable to say how far the symptoms in such cases are dependent on the action of putrefactive poisons formed in the digestive tract.

I mentioned to you at the beginning of the hour that the subject of intestinal putrefaction is still in a plastic state, and that we have a great deal to expect from further study in the field. The toxic products of putrefaction absorbed from the intestine in some severe cases of gastro-enteritis and entero-colitis, in cases of typhoid fever and in some instances of diabetes, are especially deserving of careful investigation. At present we know very little of the putrefactive products formed in these important diseases.

In the few minutes remaining to us I should like to say something about the therapeutic measures by which we strive to limit excessive fermentation and putrefaction in the digestive tract.

It is important to understand that the object of treatment is not to completely stop these processes of decomposition. To do this is not only impossible but unnecessary. What we have to do is to bring the putrefactive processes within the limits characteristic of health, and then see that they do not overstep these limits. The study of the ethereal sulphates of the urine and of special aromatic products like phenol sulphuric acid and indoxyl sulphuric acid is indispensable for enabling us to estimate the influence of treatment. Although it frequently happens that either putrefactive or fermentative processes preponderate in cases of digestive disorder, it is usual for them to be associated, and I shall discuss their treatment to some extent conjointly.

The character of the food influences in very important ways the nature and extent of fermentative and putrefactive processes in the intestine, and hence is an essential factor of any plan of treatment. It is necessary to take account of the consistence of the food and of its content of water as well as of its composition. When we wish to combat putrefactive processes the food should be soft and finely divided, since coarse and hard food-stuffs act as irritants. Thus badly

cooked cereals, the seeds of berries, kernels of corn, &c. are capable of inflicting slight traumatisms in mucous membrane already the seat of catarrhal alterations. These little traumatisms favour increased putrefaction and fermentation, perhaps chiefly because they diminish the secretion of the digestive juices, and, by slowing digestion, render the food materials more exposed to decomposition.

I think it probable that the free use of fluids with meals is sometimes favourable to putrefactive processes in the intestine. The food ordinarily contains many bacteria. If the gastric juice has an opportunity to act upon these bacteria, many of them are destroyed. If, however, the gastric juice be diluted with fluid, it is less efficacious in its bactericidal action, partly because of the dilution of the free hydrochloric acid, partly because the contents of the stomach are more rapidly passed into the intestine than where the food is more concentrated. Thus the use of fluid favours an increase in the number of bacteria that reach the intestine, and encourages putrefactive decompositions. It is therefore a good rule to restrict patients in the fluid taken with meals, in all cases where one finds the ethereal sulphates persistently in excess. This may render it desirable to exclude soups and to restrict somewhat the use of milk. The necessity for such a restriction in the volume of fluid exists wherever the free use of fluids is attended by an increased excretion of ethereal sulphates, or where it causes intestinal discomfort.

Since fermentative processes go on with especial activity in carbohydrate foods, these should be reduced where there is excessive fermentation in the gastric or intestinal contents. The restriction should not be extreme and long continued, because under these conditions it is difficult to satisfy the caloric needs of the organism. There is of course some choice as to the form in which carbohydrates should be taken. I consider that fermentative decompositions are much more likely to induce flatulence when sugars are used than when starchy carbohydrates are employed. Glucose and saccharose must therefore be avoided, and it may even be necessary to restrict the use of milk on account of its lactose. The carbohydrates in vegetables like peas and string beans may be utilised, but potatoes, bread, and most cereals should be used with great caution or not at all. The breakfast biscuits made by Huntley & Palmer are most satisfactory for use in marked cases of carbohydrate dyspepsia.

Butter may be freely used. Of the proteid foods eggs and meat are the most satisfactory.

But mere restriction in carbohydrates does not suffice for the successful treatment of excessive fermentation. The symptoms quickly disappear, but on allowing carbohydrate foods again the old symptoms return. In order to prevent this return we must improve the ability of the patient to digest carbohydrates, and this cannot usually be accomplished by merely restricting the diet.

Where the ethereal sulphates of the urine are increased either with or without an increase of the indican reaction, the dietary restrictions to be practised are quite different from those which we use in cases of simple fermentative excess. Here too, it is desirable to restrict the carbohydrates sufficiently to remove any decided symptoms of excessive fermentation that may exist, but our chief attention must be directed to prescribing the proteid food in the most suitable form. Where the ethereal sulphates are habitually much in excess the proteids should be given chiefly in the form of milk or milk foods. If we employ milk in this way we see a rapid and considerable reduction in the excretion of the ethereal sulphates, and a reduction or disappearance of the indican reaction if this has been excessive. My experience leads me to use meats only very cautiously under these conditions, since they are favourable to the continuance of excessive putrefaction. I also consider it unwise to give the nitrogenous cereals freely. Butter may be allowed in moderate or even considerable quantities, but large amounts of fat mechanically interfere with the digestion and absorption of proteids in the intestine, and are thus favourable to putrefactive decomposition.

Although much may be done by diet to diminish putrefaction in the intestine, we cannot rely entirely on this means of treatment, for in most instances the improvement from dietetic regulation is only temporary, and endures only while the proteid in the diet is chiefly milk. Our aim should be to alter the conditions of digestion so that putrefaction will be only moderate when the patient returns to a general diet. This can only be accomplished by improving the secretory conditions in the digestive tract, and for this proper exercise, rest, and various hygienic regulations are absolutely necessary.

In treating either putrefactive or fermentative disturbances

in the digestive tract it is desirable to secure for your patients food which contains only a moderate number of bacteria. The proper cooking of food greatly helps to bring about this end. Fruits or vegetables eaten raw should be carefully stripped of their coverings or thoroughly washed. Milk usually contains large numbers of bacteria. It probably makes some difference in the fermentative and putrefactive processes whether a patient drinks milk containing 1,000,000 bacteria to the cubic centimetre or only 2,000. When the milk is bottled under suitable precautions the number of bacteria may fall considerably below 2,000 to the cubic centimetre, though the number is usually larger. The quantity of proteid food ingested is an important factor in determining the extent of putrefaction. Many persons eat far more proteid than is essential to replace the nitrogenous waste of the cells of the body, and the greater the quantity of proteid eaten the greater is the opportunity for the formation of putrefactive products. It is thus desirable to restrict the quantity of proteid, and frequent small meals are to be preferred to a few large ones, not only in acute gastro-enteritis or entero-colitis, but in some instances of chronic and well-marked putrefactive disorders. It is an interesting fact that, although intestinal putrefaction does not cease during starvation, a fast of moderate duration renders it exceedingly difficult to recover micro-organisms from the mucous membrane of the stomach, duodenum, and even of the jejunum, as far down as complete emptying of the digestive canal has been effected. The importance of this fact in connection with surgical procedures on the stomach and upper part of the small intestine has been recently pointed out in an important paper by Cushing and Livingood.

The mechanical removal of micro-organisms and of fermenting food is one of the most important therapeutic resources at our command. The thorough washing of the stomach by means of the stomach tube removes from this organ a large proportion of the yeast plants and bacteria responsible for excessive fermentations. Lavage also has a distinctly beneficial influence in removing the secretory conditions that favour gastric dilatation, and, as I have already pointed out to you, dilatation strongly favours the occurrence of fermentative processes. In pronounced cases of fermentative disturbance lavage should be practised daily

with thoroughness. The beneficial effect of lavage is not limited to the control of carbohydrate decompositions in the stomach, but extends to the intestine, where fermentation is greatly influenced by the conditions in the stomach. I suspect that the improvement in the fermentative conditions in the stomach that follows lavage tends to diminish somewhat the intensity of putrefactive decompositions in the intestine, but am unable to make a positive statement with reference to this really important point.

The milder cases of fermentative disturbance due mainly to errors in diet, and perhaps to the slighter grades of dilatation, are easily brought within bounds by the appropriate limitation of the diet and the practice of lavage. Where, however, there is persistently diminished secretion of free hydrochloric acid and considerable dilatation, these measures do not usually suffice. Similarly, in the case of intestinal putrefaction, the slighter disturbances can be overcome through appropriate diet, while the old-standing and advanced disturbances call for the aid of other hygienic regulations than those pertaining to a suitable dietary. In these more serious types of intestinal putrefaction, with or without marked fermentative disorder, an out-of-door life free from worry is of the highest importance.

In many instances it is only under the prolonged influence of such a life that the nervous system regains the normal control over the digestive tract, and through the return of a physiological innervation leads to the establishment of healthy conditions of secretion and of motility. It should be the aim of the patient to increase gradually his capacity for muscular exertion, for as the powers of endurance become re-established there is also a re-establishment of the normal secretory conditions in the stomach and intestine, which is a most important protection against excessive putrefaction. It may be necessary at first for the patient to rest frequently during the day between periods of exercise. As the general strength returns the periods of rest can be diminished gradually, while the periods of exercise are correspondingly increased. As the capacity for exercise returns the dietary should be gradually enlarged, and the meat proteids may be used to largely replace the proteid of milk. Ultimately the patient should be placed on a liberal general diet, but it may be necessary for a long time to observe reasonable precautions with respect to the consistence

of the food and the use of certain carbohydrate foods such as sugars, some forms of bread, cakes, &c. Not only during the period of rest and exercise away from accustomed scenes, but also for a long time after the return to habitual occupations, is it essential to exclude emotional excitement and severe mental activity. Excited conversations, the excitements of speculative business, the emotional exhaustion following attendance on certain dramatic performances, such as Wagner's operas, sexual indulgences, and all other influences which act as a shock to the nervous system must be carefully avoided. In some instances these precautions against fatigue must be observed many months or perhaps years. The reason why we have to insist on such prolonged care is that relapse into the former state of excessive intestinal putrefaction, with its attendant exhaustion of the nervous system, is very liable to occur. I question very much if the bad cases of intestinal putrefaction are ever 'cured.' The ethereal sulphates may drop to normal under favourable conditions, but the return to a life of active industry is usually soon followed by an increase in the formation and excretion of putrefactive products, the original type of disturbance being usually re-established.

Many physicians use drugs freely—I think I may say too freely—in the attempt to control putrefactive and fermentative decompositions in the digestive tract. I shall be entirely frank with you in stating my scepticism in regard to the real utility of most of the drugs used in treating these conditions.

We have first the class of so-called internal antiseptics, including menthol, naphthaline, β-naphthol, salol, terpenthinol, camphor, derivatives of salicylic acid, derivatives of formic aldehyde, &c. Drugs of this class are used both with a view to combating fermentative processes in the stomach and to check intestinal putrefaction. I am unable to see any reasonable ground for using antiseptics to control excessive fermentation in the stomach. That many of these drugs are capable of diminishing the activity of the yeast plant and of various bacteria there is no doubt. But what excuse have you for advising their use? I have already explained to you that the main elements in the treatment of excessive fermentation are the restriction of carbohydrate foods and the removal of micro-organisms and fermenting food through the use of lavage. If you insist on the employ-

ment of these methods of treatment, which are directed against the causes of the disturbance, you will have no occasion to use antiseptic drugs, for they will be unnecessary. On the other hand if you fail to use methods of treatment directed to the causes of the symptoms, and place your reliance on drugs, you may succeed in temporarily overcoming symptoms, but you will not succeed in establishing a lasting improvement. The use of the drugs is, moreover, not without positive disadvantage. The continued dosing with antiseptics is sooner or later followed by new evidences of catarrhal gastritis, due to slight injuries inflicted on the epithelial elements of the stomach. But just as soon as we begin to inflict injuries on cell structures which we are trying to protect from the deleterious action of micro-organisms we render these cells more vulnerable to these same influences, and thus defeat our object.

Attempts to check putrefaction in the intestine by means of antiseptics are perhaps more defensible than efforts to arrest fermentations in the stomach, because it is impossible to free the lower part of the small intestine from bacteria by mechanical means such as lavage. The difficulty of such an undertaking is, however, quite evident when we consider the conditions which have to be met. In order to exert an efficient antiseptic action upon the swarm of bacteria in the ileo-cæcal region, where putrefaction is most intense, it would be necessary for antibacterial drugs to be present in considerable concentration. Efforts are often made to secure this localised action of slightly soluble antiseptics through the use of shellac or other coverings insoluble in the stomach. These efforts at enteric medication are only partly successful, for it frequently happens that the pills lose their coating too soon or not at all. Even were the action of the antiseptic confined to the lower part of the intestine, where it is needed, it would usually not be possible to introduce sufficient material to markedly diminish putrefaction without incurring a distinct risk of injuring the epithelial cells of the gut as well as the bacteria. Besides this local irritant action some of the antiseptics which, like iodoform, camphor, and turpentine, have appeared efficacious in some degree are liable to cause symptoms of intoxication.

There are two criteria by which we can form a judgment as to whether an intestinal antiseptic is really efficacious. One is the effect of the drug on the number of bacteria in the

fæces. The other is the effect on the ethereal sulphates. This latter method is inapplicable where the antiseptic is an aromatic substance capable of forming ethereal sulphates which are indistinguishable from the ethereal sulphates due to putrefaction.

Although the results derived from a study of bacteria of the fæces are conflicting, the balance of evidence appears to me to indicate that the antiseptic action of most of the drugs we employ is so slight as to be of little or no therapeutic importance. Quite recently a careful series of observations was conducted by Stern, of Breslau, with reference to the effects of β-naphthol on the fæces of a person who lived for twelve days on a diet of uniform composition. Although β-naphthol is one of the most powerful antiseptics employed for internal use, the doses of 5 grams given at first five times daily and later eight times daily had no appreciable effect on the bacteria of the fæces.

A somewhat different bacteriological test of the efficacy of calomel, salol, naphthalin, β-naphthol, and camphor has been made by introducing into the digestive tract a saprophyte, the bacillus prodigiosus, of characteristic growth and known resistance to antiseptics. It was found in the experiments which I have in mind that the organism reappears in large numbers in the fæces in spite of the use of the drugs mentioned.

In the case of calomel it has been found that after the use of considerable doses of calomel (0·3 gram) the fæces sometimes contain enough of the drug to exert a distinct antiseptic action upon the micro-organisms present, as indicated by their impaired power of multiplication.

I have observed in several instances that the use of large doses of sodium salicylate (other conditions remaining approximately unchanged) was followed by a diminution in the indican of the urine, so distinct as to leave no doubt that the diminished putrefaction was connected with the use of the drug. Many persons are unable to take 10 or 15 grains of sodium salicylate three times daily for any considerable period without developing gastric disorder, and smaller doses appear to be without distinct efficacy as regards the indican of the urine.

I think one is justified in saying that we do not know any safe intestinal antiseptic which can be relied upon to exert a distinct effect in reducing intestinal putrefaction,

much less check it. The manufacturers have shown enterprise and extraordinary assurance in putting forward the claims of their drugs as internal antiseptics, but have been usually guided more by the wish for financial success than by a desire to find out the truth. Many physicians have been induced to express opinions on the efficacy of internal antiseptics—opinions too often based on flimsy evidence. Do not therefore allow yourself to form opinions favourable to particular drugs merely because you see positive statements about them. If you cannot yourself investigate the effects of these drugs in a scientific way, do not form a judgment of their efficacy as intestinal antiseptics until some competent investigator has studied the compounds in which you are interested. Please understand that I am far from holding that there are no drugs which are capable of modifying somewhat the activity of the intestinal bacteria. I wish only to make it clear that there is at present no satisfactory evidence that the ordinary types of intestinal putrefaction can be markedly reduced by means of antiseptics. It is, however, only fair to admit that existing methods of measuring the efficacy of these drugs are so gross that slight antibacterial effects may be overlooked.

There is only one known way in which we can markedly reduce the excretion of ethereal sulphates by drugs. This is by causing free catharsis. The catharsis of calomel or of cascara is followed by a striking reduction in the excretion of the ethereal sulphates. This reduction in the sulphates is, of course, referable to diminished absorption of aromatic products of putrefaction, and this diminished absorption depends on the removal of decomposing food-stuffs and large numbers of bacteria with bacterial products from the gut. The well-known relief of headache, drowsiness, slight mental depression, &c., after purging doubtless depends on the diminished absorption of putrefactive materials. But such therapeutic measures as lead to the frequent emptying of the intestinal contents are open to the objection that they rob the organism of food materials, and thus impair nutrition. We must therefore aim to reduce excessive putrefaction, not so much by the removal of the putrefying proteids as by attaining the normal degree of decomposition through the dietetic and other measures described. Still, it is very important for you to realise that the free evacuation of the bowels is the one reliable means at present known to us of

reducing intestinal putrefaction by means of drugs, and may be especially useful in acute gastro-enteric disturbances.

It occurred to me several years ago that the character of putrefaction in the intestine might be modified, perhaps with therapeutic effects, by the introduction of certain types of bacteria with the food. My idea was that one kind of organism might perhaps interfere with the deleterious effects of another.

I found, in fact, that the introduction of large numbers of lactic acid bacilli into the jejunum in dogs was followed by a diminution in the indican of the urine. Quincke, Gans, and others in Germany have been making experiments based on the same idea. As yet the modification of bacterial activity in this way has been conducted chiefly with experimental intent, although Quincke states that the use of 15 c.c. of pure beer yeast three times daily was followed by marked diminution of the indican reaction in a human subject. One cannot but ask oneself whether the beneficial effects of kumyss and matzoon upon intestinal putrefaction are not referable in part to the micro-organisms which they contain.

Although, as you are probably aware, the native bacteria of the gut soon re-establish their preponderance after the introduction of most foreign varieties in large numbers, future studies may show us that some therapeutic advantages can be gained from the introduction into the gut of micro-organisms with different biological characters from those of the preponderant varieties of colon bacilli present where there is putrefactive excess. The actual conditions of bacterial activity are so complex and obscure in the gut that we are very far from any scientific basis for the therapeutic use of the antagonistic activities of bacteria. There is, however, one therapeutic observation which may have some significance in this connection. Where there is excessive intestinal putrefaction on a diet of milk an entire change in the proteids of the food is absolutely indicated, and meat is greatly to be preferred to milk. On the other hand, where the putrefactive excess occurs on a meat diet, a change to milk is often helpful in controlling the symptoms. It is not unlikely that these facts have their explanation in altered conditions of bacterial activity incidental to a change in the nature of the food proteid.

It is claimed that the administration of preparations of

yeast is distinctly efficacious in the treatment of boils, acne, urticaria, and other diseases of the skin commonly attended with increased intestinal putrefaction, but it is not yet clear that this contention can be sustained.

What I have told you about the treatment of excessive intestinal putrefaction applies especially to those instances in which there is an increase in the ethereal sulphates, with or without an excess of indican. I have also had in mind especially the chronic conditions which in general call for much more knowledge and skill than most acute derangements accompanied with excessive fermentation and putrefaction. We are at present unable to control those peculiar kinds of putrefaction that are associated with the appearance of cystinuria and alkaptonuria. Not only do drugs fail to exert any beneficial influence in cases of cystinuria, but even a rigid milk diet has little or no effect, if I may judge from two cases under my observation.

I hope it is clear to you that drugs have a comparatively unimportant part in the therapeutics of excessive fermentation and putrefaction within the digestive tract, and that we should place our reliance mainly on the use of suitable diet, gastric lavage, out-of-door life, and a judicious alternation of exercise and rest. Such treatment is successful because it is aimed at the removal of causes that underlie the symptoms we are trying to relieve. These symptoms are the clinical expression of derangements in the biological activities of various groups of cells, and therapeutic success can come only from what one may call the biological reformation of these cells into better habits of life. I should like to have you think of the chronic disorders dependent on altered states of micro-organic activity in the alimentary tract as arising from the long-continued and cumulative influence of many unfavourable biological influences due to erroneous habits of life. Many of these influences unfavourable to the normal life activities of the cells of the organism are individually of little importance, but collectively become highly efficient causes of disease. I should also like to have you think of successful treatment as consisting in the reversal of this process, and as dependent on the gradual accumulation of little biological advantages accruing from improved habits of life.

I consider it highly important that you should explain to your patients the causes of their disorders and the rationale of your plan of treatment. Very few of the laity, even of

the educated and well-to-do classes, have correct ideas of the causes of digestive derangements of which we have been speaking. They are ignorant of biological laws, and therefore cannot understand the necessity for practising the self-denial which is often so necessary to secure a permanent improvement in health. It is therefore your duty to somewhat educate them to modern ways of thinking about the nature of the disorders we have been discussing. Your best efforts will prove useless, however, in many instances. A large proportion of people are sensualists whom you cannot restrict in their food and drink and sexual activities without depriving them of the things for which they chiefly value life. They are unwilling to practise even reasonable curtailment of their harmful physical pleasures—often the only pleasures known to them. They do not want a physician who has the knowledge to prescribe a rational plan of treatment, and the force of character to insist that it be carried out. What they want is a magical pill which will cure them while they continue to sin against biological laws. Do not try to keep patients of this kind; let them go to those who will promise to cure them with drugs. If you do this you will preserve your peace of mind and your self-respect. But you will also find that there are many persons who value sound advice, even if it leads to some restriction of their physical pleasures.

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LECTURE VIII

THE CHEMICAL PATHOLOGY OF GASTRIC DIGESTION

Frequency and importance of disorders of gastric digestion—Disorders of salivary digestion—Increased salivary secretion; diminished salivary secretion—Qualitative changes in the saliva—Influence of gastric disorders on general nutrition—Effects of starvation—Disorders of gastric secretion; of motility—Conditions requisite for the secretion of hydrochloric acid; chlorine content of blood, intact epithelia, and normal innervation—Pawlow's experiments—'Psychical and pseudo-feeding'—Effect of mental and physical fatigue—Combined and free hydrochloric acid—Uses of free acid—Symptoms and other effects of diminished secretion of hydrochloric acid—Significance of absence of combined hydrochloric acid—Symptoms and other effects of hyperchlorhydria—Symptoms and nature of gastroxynsis or gastro-succorrhœa periodica—The ferments of the gastric juice—Nature of their secretion—Secretion of these ferments largely independent of the secretion of hydrochloric acid—Explanation of this independence—Secretion of water of the gastric juice—Therapeutics of disorders of gastric secretion—Hygienic measures—Influence of diet—Use of drugs—Therapeutic use of ferments—Disorder of gastric secretion attended by excessive secretion of mucus; mucous gastritis—Disorders of gastric motility—Increased motility—Decreased motility—Gastric atony and dilatation—Pyloric stenosis—Symptomatic effects of dilatation—Distinction between malignant and non-malignant stenosis—Relation of Reichmann's disease to dilatation—Treatment of dilatation—Relationship between disorders of motility and disorders of secretion.

At our last two meetings we discussed, with some attention to detail, the fermentative and putrefactive processes that go on in the digestive tract. This morning I propose to consider the chemical pathology of digestion from a regional point of view, and with special reference to the various secretory derangements which we observe in the stomach and in the intestinal tract.

You will find on entering practice that a large proportion of your patients have derangements of digestion, and your success in treating these conditions will depend very largely

on your intelligent understanding of them. The day has gone by for treating digestive disorders purely on symptomatic grounds. In order to treat your patients rationally and successfully you must acquaint yourselves with the conditions which exist in individual cases, and this can be done only by painstaking study. The disorders of digestion are important, not only in their immediate effects on the body, in the production of local symptoms, such as nausea, gastric pain, constipation, &c., but for their remote effects on the entire organism. Such disorders may lead to changes in the composition of the blood, in the nutrition of the tissues generally, in the functions of the nervous system, and in the work of renal excretion. I cannot impress on you too strongly the fact that patients are not always conscious of derangement in their digestive processes. Many of them will confidently tell you, when questioned on the subject, that their digestion is very good, and if you give credence to their statements you will overlook important conditions, merely because these conditions happen not to give rise to obtrusive symptoms. One other fact of a general character I must bring clearly to your notice. Patients will frequently come to you suffering from diseases not directly connected with digestive disturbance, as, for instance, chronic nervous disease, like locomotor ataxia, or valvular disease of the heart, or small granular kidneys. You will find in many of these patients that the therapeutic results will be very limited if you direct your attention wholly to these well-developed organic lesions. If, however, you take the trouble to consider with care the state of the digestive tract, you will find very frequently that there are disturbances going on which it is well worth while to remedy. And through the removal of such digestive disorders you will frequently exert a distinctly beneficial effect upon the organism at large and upon the particular conditions for which your patient in the first instance consulted you.

In what I have to say about the chemical pathology of digestion it will be convenient to speak, first, of the digestion that is initiated in the mouth under the influence of the saliva ; secondly, about gastric digestion ; and thirdly, about digestion as it goes on in the intestine.

A thorough insalivation of the food is of considerable importance for the digestive process, since it helps the mechanical division of the food, favours the conversion of

starch into maltose, and cleanses the mouth. The most important chemical influence of the saliva is that which it exerts in the energetic conversion of starch into maltose, an action discovered so recently as 1831.

The normal saliva contains epithelial and wandering cells, probably phagocytic, mucin, albumin, the ferment ptyalin (which converts starch into maltose), chlorides, bicarbonates, alkaline phosphates, and traces of sulphates and of sulpho-cyanic acid (CNSH). It also contains oxygen, nitrogen, and carbon dioxide in solution. The solids of the saliva amount to 5 or 10 per cent. The specific gravity is low, and varies from 1·002 to 1·009. The reaction, though generally alkaline, is frequently neutral or acid, especially a few hours after meals and at night. In a healthy adult the amount of saliva secreted in the course of twenty-four hours varies considerably, but is usually from 500 to 1,200 c.c. In proportion to the weight of the body the secretion is much greater in childhood than in adult life.

Although we cannot sharply separate the quantitative and qualitative alterations in the saliva, it is convenient to consider them individually. A state of increased salivary secretion is by no means uncommon. Such an increase arises in various ways. The irritation of sensory nerves is capable of stimulating the secretory activities of the salivary glands. We see this in diseases of the mouth, during dentition, in gastric disorders, in neuralgias of the fifth nerve, in pregnancy, during hunger, and under the influence of the sight of food. Another cause of increased salivary secretion is the irritation of cerebral centres, as in suffocation. Certain poisons, such as mercury, pilocarpin, nicotine, and muscarine, are capable of stimulating the flow of saliva. Some diseases of the central nervous system, as bulbar paralysis, general paralysis of the insane, and other chronic insanities, epileptic seizures, &c., may be associated with a considerable degree of salivation. In slight fevers also there may be an increased secretion.

Derangements of gastric function are sometimes the unsuspected cause of persistent ptyalism. Dr. S. W. Lambert tells me of a pregnant woman in whom a very abundant salivary flow resisted all the usual therapeutic measures and caused marked impairment of nutrition. The long-standing ptyalism quickly ceased after the practice of gastric lavage was begun, and did not return.

A diminution in the salivary secretion results in a variety of ways. Mechanical obstruction of the excretory duct of a salivary gland belongs to the exceptional causes of diminished salivary secretion. The obstruction is sometimes the consequence of salivary stones, which are usually made up of calcium and magnesium phosphate and calcium carbonate. These stones grow concentrically, usually about epithelial cells or masses of leptothrix as a nucleus. Their importance is slight, as they give rise only to local symptoms. In various febrile states, such as typhoid fever, pneumonia, phthisis, &c., there is commonly a decrease in salivary secretion, and the saliva is sometimes acid in reaction. The action of the saliva on starches is then usually reduced in the sense that the quantity of starch that can be converted in a given time is diminished. But the converting action of a given amount of saliva may not be decreased in fever, or may even be increased. Any condition which leads to loss of water from the organism gives rise to diminished secretion of saliva. This effect is seen in ascites, cholera, and diabetes. The loss of water may also explain the diminished secretion noted in cases of extreme dilatation of the stomach. Severe fright is sometimes followed by a reduction in salivary secretion.

Alterations in the quantity of salivary secretion do not as a rule exert much influence on the digestive processes, since even the complete absence of salivary digestion seems to be readily compensated by the pancreatic juice. The prolonged loss of large amounts of saliva has been known to be followed by very rapid and considerable loss in weight, but instances of this sort belong to the curiosities of medicine.

There are a few facts regarding qualitative changes in salivary secretion which it is desirable for you to keep in mind. Thus in mercurial salivation the secretion may contain much more mucin than normal. In fever the sulpho-cyanic acid is often absent, and owing either to the acid reaction or to the absence of ptyalin there is little or no action upon starch. As the pancreatic secretion is apt to be similarly checked it is well for you to largely withhold starchy food during acute fever. It is said that tobacco smoking causes an increase of sulpho-cyanic acid in the saliva, but it is unknown whether this has any clinical significance. The sulpho-cyanic acid is also said to be increased

in rheumatism and nephritis. Urea may appear in the saliva in various forms of renal disease associated with the accumulation of an excess of urea in the blood. It is possible that this fact may some day be utilised in recognising renal insufficiency for urea. As yet physicians have not turned it to practical account. In diabetes the saliva may have an acid reaction, but does not contain sugar. In anæmic states the saliva grows poor both in mineral and organic constituents. In jaundice the bile pigments do not enter the saliva, and the patient is fortunately spared an unpleasant bitter taste. Alcohol passes readily into the saliva in some patients, and the story is related that a patient who had prohibitionist scruples was surprised to recognise the taste of brandy in his mouth soon after he had been given an enema containing it. In cases of hydrophobia the poison has been found in the saliva three days before the dog gave symptoms. The readiness with which some salts, *e.g.* the iodides, enter the saliva after absorption from the stomach has been practically utilised to determine the quickness of absorption from the stomach. Where this absorption goes on normally iodide of potash is found in the saliva about fifteen minutes after its administration. In patients with gastric dilatation and slow absorption a much longer time may elapse before iodine can be detected in the saliva.

The most important alteration in the character of the saliva has to do with its content of ptyalin as expressed by the capacity of the saliva to convert starch into substances which, like maltose and dextrose, reduce Fehling's solution. Recent observations made by Robertson on the saliva in health and disease indicate that we may take 0·080 gram of sugar, produced by the action of 2 c.c. of saliva on 10 c.c. of starch for ten minutes, as a low average of activity for healthy adults. The average in the case of children varying in age from sixteen months to thirteen years was 0·078 gram of sugar. The same observer noted that there is a decrease in the salivary activity in most cases of gastro-enteric disease, but that there may be an actual increase in some instances of 'acid dyspepsia.' The salivary ferment appeared to be absent in one case of great dilatation of the stomach. It was also reduced in many diseases of the nervous system, in Addison's disease, and in many patients with renal disease. On the other hand, in three out of four

cases of diabetes the proportion of sugar formed by the saliva is said to have been much in excess of the average normal.

While it is true that the action of ptyalin on starch is checked by the destructive action of the gastric juice upon the ferment during the period of full proteid digestion there is reason to think that the process of salivary digestion is not confined to the mouth and is not so quickly terminated in the stomach as is generally taught. Free hydrochloric acid does not appear in the stomach as a rule until after the lapse of three-quarters of an hour, and during this time there is doubtless an active conversion of starch. Indeed, this period of starch digestion may be somewhat longer, since a trace of free acid favours the amylolytic action.

Where the amylolytic action of the saliva is regularly lowered, and there is excessive fermentation in the stomach, it is wise to restrict the quantity of starch-holding food, or to make use of ferments like taka-diastase.

The acid reaction of the saliva observed in fever, in diabetes, in some digestive disorders, and in the presence of the thrush fungus has been thought capable of exerting an injurious action on the teeth where the condition persists for a long period. Cases of dental caries have been ascribed in part to the action of acid fluids in the mouth, but a critical examination of the evidence does not justify us in assuming that there is any necessary or constant relationship between caries and the altered reaction of the buccal fluids.

I shall now sketch for you some of the leading pathological conditions that are connected with derangements in the chemistry of gastric digestion. I believe one may safely say that disorders of gastric digestion unaccompanied by deranged intestinal digestion are comparatively rare. It is common, however, for evidences of derangement in stomach digestion to precede the evidences of derangement of digestion in the intestine.

Considerable disorder in gastric digestion is consistent with little impairment in general nutrition. There are, indeed, persons in whom the stomach appears to perform little or no digestive work, and in whom intestinal digestion is carried on in such a way as to maintain a good state of general nutrition. Still we may say that sooner or later all chronic disturbances of the secretory or motor functions of the stomach lead to some impairment in general nutrition.

Sometimes this impairment is so great as to endanger life. Diseases of the stomach impair nutrition partly through the inability or dislike of the patient to take food in sufficient amounts. In many patients with acute and chronic gastric catarrh with carcinoma &c. there is decided loss of appetite. The fear of pain is a frequent cause of a diminished intake of food, for, as you know, patients with gastric ulcer, with hyperacidity, and with some varieties of nervous dyspepsia, are very liable to experience sharp paroxysms of pain after eating. Vomiting and nausea also act as powerful deterrents. We see this in many instances of gastric catarrh and in some cases of ulcer and carcinoma. All these causes lead to the same result: the patient takes insufficient food, and in order to meet the necessary caloric expenditure pertaining to the cell activity of the body lives on his own tissues to a considerable extent. Loss of weight and strength is the inevitable result.

In acute disease of the stomach, as gastritis or gastro-enteritis, there may be absolute starvation during a variable but usually short period. The metabolism of the body then takes on the characters belonging to inanition. This subject I shall discuss with you at another time, although I may mention here the highly characteristic fact that the urine contains very little sodium chloride under these circumstances. The great losses in weight which we sometimes see in these acute diseases of the stomach need not in themselves cause you concern. They are quickly repaired during convalescence. I have found it most difficult to teach parents that children suffering from acute gastritis should be permitted to starve for twenty-four, thirty-six, or forty-eight hours. They are apt to think that their children will waste away and die in consequence of the deprivation of food, while in reality rest is the most essential feature in the treatment of many of these acute conditions. You will only occasionally meet with cases of acute disease of the stomach in which temporary starvation cannot be well borne for one or two days. I may add that it is a very common mistake to begin feeding patients too soon after the onset of acute gastritis.

The losses in weight which occur slowly in the course of chronic affection of the stomach are far more serious. They indicate that the cells of the gastric mucous membrane and perhaps those of the small intestine have fallen into per-

sistently bad habits of activity, and that a long period of time will be required to correct these disturbed functions. In most instances of disease of the digestive tract the loss of weight can be attributed to the diminished utilisation or diminished absorption of food materials. There appear to be instances, however, in which this explanation does not fully explain the loss in weight; that is to say, cases in which the patient should hold his weight better considering the quantity of nitrogen absorbed. Here some other influence than starvation is thought to be at work, and it is not improbable that a portion of the weight lost is to be attributed to the action of poisons absorbed from the stomach or intestine.

In considering the chemical pathology of gastric disorders, it is convenient to distinguish between those derangements connected with disturbed secretory activity of the stomach and those in which the motor as well as the secretory functions are implicated. A practical reason for this distinction is that the consequences to the organism are commonly much more severe in the latter than the former class of derangements.

In a condition of health the mucous membrane of the human stomach secretes gastric juice in large amount in the twenty-four hours, 1,200 or 1,500 cubic centimetres being probably not far from the actual quantity. The gastric secretion contains some epithelial cells and a small quantity of mucin, but a normal mucous membrane secretes little mucus. In disease the amount of mucus may be much increased. The pathological secretory activity of the stomach which leads to a marked increase of mucus is something quite distinct from the secretory activity which produces the gastric juice, and we shall have to consider it separately.

Although the gastric juice contains traces of proteid and mucin, mineral chlorides, and traces of phosphates and iron, its important constituents as a digestive secretion are its hydrochloric acid, its ferments (pepsin and rennin), and its water.

Physiologists and clinicians have devoted much attention to the study of the conditions under which the hydrochloric acid of the gastric juice is secreted, but the physico-chemical details of the process are still obscure. For our present purpose it is sufficient to recognise that there are three essential requirements for a secretion of hydrochloric acid. One of

these is the presence in the blood of certain substances capable of yielding chlorine, a second is the functional and structural integrity of the acid-forming cells of the gastric glands, and the third is the maintenance of an intact regulatory nervous mechanism. The failure of any one of these elements impairs or abolishes the capacity of the stomach to secrete hydrochloric acid.

The constituent of the blood which is essential for the production of hydrochloric acid is chlorine, which exists as chlorides. In speaking of the salts of the organism, I mentioned the rôle of the chlorides in yielding the chlorine for the formation of hydrochloric acid, and spoke of the reaction which is supposed to occur in the glandular cells between the ions of dissociated sodium chloride and those of the hypothetical mono-sodium phosphate furnished by the blood. Whatever may be the method by which the hydrochloric acid is formed, it seems clear that we must recognise specific functional activities in the epithelial cells by which they effect the separation of the acid to the formation of which a disruption of the chloride molecules is an essential part. How important are the chlorides for the formation of the acids of the gastric juice is readily shown by experiment. Reduce the chlorides of the organism either by withholding chlorine from the food or by causing its excessive excretion, and the secretion of hydrochloric acid in the gastric juice promptly ceases. A gastric juice is formed containing ferments but no acid. This is because the blood holds its chlorine so tenaciously, when its concentration in chlorine ions is reduced, that the gastric cells are no longer able to secure the chlorine necessary to make the normal acid. If now one introduces chlorine directly into the circulation, say as calcium chloride, the secretion of an acid gastric juice promptly returns. We can thus understand why very free sweating is followed by a temporary diminution in the hydrochloric acid of the gastric juice, and why the ingestion of the chlorides in mineral waters stimulates this secretion. We can also understand why the stomach should fail to secrete hydrochloric acid in all states of disease accompanied by a marked diminution in the food supply.

The diminution of the chlorides in the organism is, however, seldom sufficient to explain the frequent loss or diminution of acidity of the gastric juice which we meet in disease. Even in advanced anæmias and carcinomatous cachexias

there may be a secretion of hydrochloric acid, if there is not also a state of chronic inanition. In the great majority of such derangements of function the cause is to be sought either in changes in the glandular cells or in the regulating nervous mechanism. Structural alterations in the glandular apparatus of the stomach are capable of impairing the secretion of hydrochloric acid. If the acid-producing cells of the mucous membrane are acted on by irritants capable of inducing gastritis, or the glandular apparatus be the seat of carcinomatous infiltration or an atrophic process, these cells fail to produce hydrochloric acid, or produce it only in diminished amount. When one remembers that the secretion of hydrochloric acid necessitates specific cell activities of a complex nature, it causes no surprise that structural alterations in the secretory cells may wholly and permanently abolish the activities necessary to produce this secretion. One can also imagine that slighter structural alterations and even functional disorders might lead to impaired secretion.

In some instances of gastric disease the glandular structures of the mucous membrane are proliferated, and the acid-forming or oxyntic cells are increased in number. One might almost predict that under these circumstances the amount of hydrochloric acid secreted would show an increase. There is in fact such an excessive secretion, and many cases of hyperchlorhydria are associated with glandular alterations of the kind to which I have just referred.

The third essential to the secretion of hydrochloric acid is an intact nervous mechanism. It was formerly supposed that the chief influence in the secretion of gastric juice containing hydrochloric acid is the direct mechanical irritation of the mucous membrane by the food. To nervous influences was ascribed a wholly secondary rôle. But we now know that the mere mechanical irritation of the mucous membrane, as by the introduction of pebbles or other indigestible material into the stomach, is followed by little or no secretion of gastric juice. On the other hand, there is unequivocal evidence that the nervous system is closely concerned with the secretory act. The ingenious experiments of Pawlow in this connection should be known to you. Pawlow and his pupils isolated the stomach in dogs in such a way as to readily study the secretion of gastric juice. At the same time the œsophagus was divided transversely and the cut ends were attached to openings in the neck. Through one

of these openings food taken by the mouth could escape without entering the stomach; through the other opening in the neck food could be introduced into the stomach without first passing through the mouth.

In animals thus prepared various influences of food were studied. Thus food was shown the animal without allowing it to enter the stomach. Under the influence of this so-called 'psychical feeding' the stomach secreted normal gastric juice. In the second place the animal was allowed to eat food which did not enter the stomach, but passed out of the œsophageal opening. In this 'pseudo-feeding,' as in the psychical feeding, the stomach secreted gastric juice. The secretion in each case is reflex in character. It was further found that when the secretion of gastric juice is stimulated by the direct introduction of food into the stomach through the œsophageal opening—without the knowledge of the animal and without the action of the saliva—the period which elapses before the secretion begins is almost the same as in the case of the psychical and pseudo-feeding.

The experiments of Pawlow and his pupils prove that nervous impulses carried to the mucous membrane of the healthy stomach are highly effective in bringing on the secretion of gastric juice containing hydrochloric acid. The route along which these efferent secretory impulses pass is chiefly the vagus. This is shown by the behaviour of secretion under various influences affecting the vagus nerve. If we cut the vagi in a dog, reflex secretion no longer occurs. But if we stimulate electrically the peripheral ends of the cut nerves some twenty-four hours after their section there is soon a flow of gastric juice. The short delay observed before the establishment of the flow is doubtless due to metabolic changes taking place in the glandular cells of the stomach. Section of the splanchnic nerves apparently does not affect these results of section and stimulation.

Although it still remains for physiologists to clear up some points connected with the nervous influences that affect the secretion of the hydrochloric acid of the gastric juice, it is easy to understand from what I have already told you that great mental or physical fatigue should be capable of depressing this secretory function. Observation teaches us that the secretion of free hydrochloric acid is depressed in many persons after a period of worry or excitement, after unusual muscular fatigue, or after sexual excitement. There

are, of course, wide individual variations in respect to the effectiveness of these different influences, which we are at present unable to explain satisfactorily. Thus it is difficult to say why it is that apparently the same depressing nervous influences which in most persons cause a diminished secretion of hydrochloric acid give rise in a few individuals to an excessive secretion of this acid. If you recognise the disturbing effects exerted through the nervous system on the secretion of hydrochloric acid, you will be able to advise your patients much more intelligently than if you ignore these nervous influences.

The observation that the sight of food excites a reflex secretion of gastric juice is not without practical importance. It emphasises the necessity for food that is prepared and served in an appetising manner. The keen insight of Shakespeare into matters physiological long ago found expression in the words of Macbeth, 'Now good digestion wait on appetite, and health on both!' and modern investigation teaches us that anything which impairs the appetite also impairs the capacity for gastric digestion, probably by reducing the secretion of hydrochloric acid.

The hydrochloric acid in the gastric juice normally exists there in three different forms. First, in combination with bases as salts, like sodium chloride; second, in combination with proteids; and third, as free acid. The salts of hydrochloric acid, such as the sodium and potassium chlorides, probably have no part in the digestive process excepting in so far as they may influence it through their physical properties or through furnishing chlorine to the blood. The acid combined with the proteids of the food is of far more significance for gastric digestion, because the formation of these acid products is a step in the digestion of proteids preceding the formation of albumoses and peptone. In a state of health proteid food in the stomach always calls forth a secretion of hydrochloric acid proportioned to the requirements of the food. At first all the acid secreted under the direct and reflex stimulus of the proteid combines with this proteid. After a time, however, so much acid is secreted that there is an excess above the amount required to combine with the albumins, globulins, or other proteids. In other words 'free' hydrochloric acid makes its appearance. As one might expect, the greater the amount of proteid the longer will be the interval preceding the appearance of free

acid. After a meal of moderate size the free acid does not appear for twenty minutes or half an hour.

Since it is thus a feature of healthy digestion that the stimulus of proteids to the epithelial cells is sufficient to ultimately call forth the secretion of free acid, no matter how abundant the proteid, it is natural to infer that the free acid is helpful to digestion. We have abundant evidence that this is really the case. The free hydrochloric acid of the gastric juice possesses some bactericidal action, as I have already explained to you in speaking of the chemical defences against disease. It also has the power of converting the bodies called proënzymes—the antecedents of the ferments pepsin and rennin—into these bodies themselves. It is not clear that this action of hydrochloric acid is absolutely essential to the conversion of the proënzymes, but it is likely that the entire absence of combined acid is a grave hindrance to digestion in consequence of failure in the function of transforming the proënzymes into active ferments. Although hydrochloric acid helps to bring about the inversion of sugar, this can hardly be regarded as an important function. The anti-fermentative action of the acid undoubtedly protects sugar from decomposition, and thus the acid is indirectly helpful to the digestion of this type of food. It is thought by some writers that the free hydrochloric acid has an important function in the regulation of the movements of the stomach, and that the absence of the acid favours atony. Still another action of the free acid is to bring into solution the calcium and magnesium salts of the food through the formation of the chlorides of these elements. This function is probably one of considerable importance to the growth of bone. Finally hydrochloric acid is a powerful physiological stimulus to the secretion of the pancreatic juice.

From what I have just told you of the functions of free hydrochloric acid in the gastric juice one would expect various disorders of digestion to arise when the secretion of free acid ceases or is greatly reduced. We know from observation that when the percentage of free acid in the gastric juice is generally below 1–1·8 part in the thousand slight symptoms of gastric disorder are often present. The commonest of these symptoms are loss of appetite, slight nausea, a little discomfort in the epigastric region after eating, and an inclination to the excessive fermentation of sugars and starches. But it is important for you to know that the

amount of free acid may be much below the normal without any obtrusive clinical manifestation of disordered digestion. This is doubtless due to the fact that gastric digestion is carried on with diminished acid by means of the ferments of the gastric juice, which, as I shall soon point out to you, are not usually reduced in proportion to the reduction of the acid.

When there is no secretion of free hydrochloric acid whatever, disorders of gastric digestion are seldom wanting: excessive fermentation is apt to be pronounced, and sooner or later the stomach grows atonic and dilatation occurs. Moreover, in time the signs of excessive intestinal putrefaction develop, and this condition brings in its train a variety of chronic disturbances, some of which I have sketched for you in previous lectures.

But the entire absence of free hydrochloric acid from the gastric juice has not always the same significance. It is essential to distinguish between those cases in which there is still some acid in the combined state—that is in union with proteids—and those cases where no hydrochloric acid whatever is secreted or the amount of the combined acid is very low.

The regular and complete absence of combined hydrochloric acid as well as free acid is always an indication of well-defined structural changes in the glandular apparatus, and should lead us to suspect atrophy of the gastric mucosa, an advanced gastric catarrh, or carcinoma. When, on the other hand, there is a fair amount of combined acid, there is always the possibility that the disturbance is dependent on nervous influences, notwithstanding free acid may be absent regularly or much of the time. In the latter class of cases the outlook for restitution of function is good because it is possible that the improvement in nervous tone will be followed by the reappearance of free acid.

It was formerly claimed that the absence of free hydrochloric acid in the gastric juice is a certain indication of gastric cancer. We now know that while it is a very frequent accompaniment of carcinoma there are many other states in which there is no secretion of free acid—cases of acute chronic gastritis, diabetes, anæmia and tuberculosis, febrile states, neurasthenic conditions, chronic nephritis, and conditions of extreme dyspnœa. Nevertheless the persistent absence of free acid should lead one in every instance to consider carefully the question of gastric carcinoma and to look for other indications of its presence.

The loss of free hydrochloric acid in cancer, with or without the presence of acid in the combined state, has been attributed by some writers to coexistent chronic gastritis, by others to atrophy of the gastric tubules due to the new growth, and by still others to the neutralisation of the acid by the toxic products of the cancer cells. I think the evidence relating to this point indicates that the loss of the acid-producing functions of the gastric glands is due in part to the infiltration of the new growth, in part to the associated gastritis, and in part to nervous influence. In cases where this function is lost there is generally extensive gastritis, even when the new growth is not widely diffused. On the other hand it has been often noticed in the exceptional cases of gastric carcinoma in which free hydrochloric acid is excreted throughout the course of the disease that the new growth is not extensive or that gastritis is not well developed. In some instances the growth involves a part of the stomach, the pyloric extremity, in which the glands do not normally secrete hydrochloric acid.

The term 'hyperchlorhydria' is applied to those not uncommon cases of secretory disturbance in which hydrochloric acid is regularly secreted in excess. What constitutes an excess is a point on which writers are not entirely agreed, but it is probably safe to say that a gastric juice which one hour after a test breakfast contains more than 0·3 per cent. of free hydrochloric acid is pathological even if symptoms be temporarily absent. The highest percentage of free hydrochloric acid that I have observed one hour after a Ewald test breakfast is 0·7 per cent.

Symptoms are rarely wanting where the percentage of free acid exceeds 0·4 per cent. They consist of epigastric pain developing one or two hours after a meal, epigastric tenderness, and constipation. Sometimes the pain is mainly neuralgic in character; usually it is described as continuous and burning. Whatever the nature of the pain, it has the peculiarity of being temporarily relieved by proteid food, which ties the free acid, but ultimately stimulates secretion to a point where the acid is again greatly in excess. Pain may be felt in the region of the left scapular angle. The general health does not suffer at first, but after a time there is apt to be loss of weight and strength in marked cases.

I have observed a decided retraction of the gums from the teeth in many of my patients with hyperchlorhydria.

There are certain effects of an excessive secretion of hydrochloric acid upon the digestive processes which require mention. One of these effects is an increased rapidity in the formation of albumoses. While such an action has been observed in some cases, it appears to be by no means a constant effect of hyperchlorhydria. On the other hand, the action of the ptyalin of the saliva is retarded, since this ferment is not active in a strongly acid medium. The digestion of starch may be checked within a few minutes after the food enters the stomach, for the free acid can sometimes be detected so early as ten minutes after a test breakfast. When the acidity of the gastric juice in hydrochloric acid exceeds 0·6 per cent. it is thought that even the digestion of proteid foods is retarded.

The effect of hyperchlorhydria on intestinal digestion has not been sufficiently studied. The excess of acid probably retards the digestion of starches, but it is not clear that it interferes with the digestion of the fats. It is supposed by some that the delay in the appearance of an alkaline reaction in the contents of the small intestine induces the constipation often noted in hyperchlorhydria by slowing digestion.

The gastric pain in excessive acidity is sometimes caused by contractions of the pyloric muscles, and these contractions may lead to fatigue and atony of the stomach, and perhaps to dilatation. I shall refer again to this effect of the excessive acid in speaking of the disturbances of gastric motility.

There is one disturbance of the secretory function of the stomach which strikingly illustrates the relationship between the nervous system and the production of the hydrochloric acid of the gastric juice. This is the state known as gastroxynsis or gastro-succorrhœa periodica. In this neurosis of secretion the patient from time to time suffers from very acute seizures of headache, pyrosis, nausea, and vomiting. There is severe thirst, and prostration soon sets in. The vomit consists of strongly acid mucous masses, and contains a high percentage of hydrochloric acid. A singular feature of these seizures is that they commonly develop while the stomach contains little or no food, often in the middle of the night or towards morning. The quantity of gastric juice that is vomited in seizures of this character is sometimes 500 c.c. or 600 c.c., and the vomiting may recur several times in the course of a day.

Although we have no wholly satisfactory explanation of these remarkable seizures, their neurotic character is strongly suggested by the fact that they develop almost exclusively in persons subjected to severe mental or emotional strain, and cease, temporarily at least, after a period of rest and freedom from taxing mental effort. Bearing in mind what we know about the relation of the vagus nerves to the secretion of hydrochloric acid, one is tempted to regard this state of gastroxynsis as dependent on some disorder of the nervous system in which the vagi are the conductors of excessive stimuli to the acid-forming cells of the glandular apparatus of the stomach.

Having now discussed with some detail the conditions in which there is a disturbed secretion of the hydrochloric acid of the gastric juice, I wish to say something about the secretion of the ferments of the gastric juice.

The human gastric juice contains at least two apparently distinct ferments, pepsin and rennin. Pepsin is a proteolytic ferment capable of converting proteids into albumoses and peptones. Rennin, the rennet ferment, causes the coagulation of milk by converting the caseinogen into casein in the presence of calcium salts. While both these ferments are secreted in the gastric juice the glandular cells from which they come apparently do not hold them in any considerable quantity, but contain substances called proënzymes, from which they are produced. These proënzymes, pepsinogen and rennet zymogen, probably exist in considerable amount in the granules of the chief cells of the gastric glands, even when the stomach is not secreting gastric juice. An important factor in the conversion of pepsinogen and the rennet zymogen into pepsin and rennin respectively is probably the hydrochloric acid of the gastric juice. This conversion occurs with great rapidity. Thus it was found that all the pepsinogen present in the aqueous extract of a cat's gastric mucous membrane could be converted into pepsin in sixty seconds by treatment with 1 per cent. hydrochloric acid.

The presence of free hydrochloric acid in the human gastric juice is apparently not essential to the conversion of the proënzymes into the ferments themselves. At least we know that the gastric digestion of proteids sometimes proceeds with normal activity where none of the free acid can be detected. On the other hand, where there is no

secretion whatever of hydrochloric acid there is probably no peptic activity; but this activity is sometimes considerable where the amount of combined hydrochloric acid is very low. How is the conversion of the proënzymes into the ferments effected when no free hydrochloric acid is detectible? I do not know of any evidence bearing on this point, but it seems to me not unlikely that hydrochloric acid may still be effective in producing the ferments from the proënzymes without being secreted in sufficient amount ever to be present as free acid.

The rennet ferment can be separated from the proteolytic ferment pepsin by chemical means. Thus where the two ferments are present the gradual addition of lead acetate precipitates the pepsin sooner than the rennin. Similarly the proënzyme pepsinogen can be distinguished from pepsin itself by a chemical procedure. The reagent used to effect this separation is sodium carbonate. This salt has a powerfully destructive effect on pepsin, but a much less decided action upon certain extracts of the gastric mucous membrane from which pepsin can be derived by appropriate treatment, and which are therefore assumed to contain the pepsinogen.

I just now mentioned that the gastric digestion of proteids may continue when there is no secretion of free hydrochloric acid. There is in fact no close relationship between the amount of free acid and the amount of pepsin as measured by its proteolytic activity. Both entire absence of free hydrochloric acid and its presence in considerable excess are compatible with a normal activity of the pepsin ferment. The independence of the two functions, the ferment-secreting function and the hydrochloric acid-secreting function, is well illustrated by the conditions observed in some cases of non-malignant stenosis of the pylorus. It can be demonstrated without much difficulty in some of these cases of stenosis that the irritant products of fermentation in the stagnating food excite the gastric glands to the secretion of an excessive percentage of hydrochloric acid in the gastric juice. This excess of acid does not develop immediately after the meal, but after a period of stagnation. The overaction of the acid-forming cells is followed by a depression of function in the acid-making cells during which little or no secretion of free acid is observed. Now the fact which I wish to emphasise here is that during these

marked fluctuations in the secretion of acid the secretion of pepsin ferment continues with no marked fluctuations, and apparently unaffected by what is happening in the disturbed acid-forming cells.

I do not wish to give you the impression that the pepsin-secreting function of the stomach is never disturbed. This function, though much more stable than the acid-forming function, is sometimes greatly depressed. Thus in any condition attended by extensive glandular atrophy the peptic function may be greatly impaired or may wholly fail. We see this in cases of carcinoma, in cases of pernicious anæmia, and in the state known as achylia gastrica, in which little or no gastric juice is formed. When there is a rapid and persistent loss of peptonising power, which develops under repeated observation in a patient who secretes no free hydrochloric acid, the ground for suspecting carcinoma becomes very strong. Whether the ferment-making function of the gastric cells is ever lost where the acid-forming cells continue to secrete acid normally is a point on which I cannot inform you. So good an observer as Hammerschlag states that in nervous dyspepsia the peptic action may be greatly depressed while the secretion of acid is normal, but further studies are desirable.

The want of parallelism between the peptic and acid functions in the same individual is also observable in studies of the action of drugs. Thus Shiff found that atropin not merely diminished the quantity of the gastric secretion, but often lowered the percentage of hydrochloric acid without depressing the peptic activity.

How are we to explain the absence of parallelism between the acid-forming and the pepsin-forming functions of the stomach? The answer to this question is to be sought in the difference between the process of pepsin production and secretion and the process of acid production and secretion.

Carefully conducted observations indicate that the gastric mucous membrane in the dog contains more pepsin or pepsinogen during the fasting state than during digestion, and that the pepsin or pepsinogen content falls gradually as the digestive process advances in the stomach. The formation of the ferment thus occurs at a time of rest on the part of the secretory mechanism of the peptic cells, and this formation of pepsinogen is apparently the result of a direct

transformation of the cell protoplasm. After a sufficient period of rest the glandular cells are loaded with pepsinogen, and probably all that is required to bring about an abundant secretion of the ferment is the necessary nervous stimulus and the presence of a small amount of hydrochloric acid.

The formation of the proënzymes in the glandular epithelia appears to be closely connected with the supply of oxygen. During the period of secretory rest in which the proënzymes are formed, the stomach is anæmic and the epithelial cells receive little oxygen. This diminution of oxygen doubtless hastens the decompositions in the cell protoplasm which result in the production and accumulation of the proënzymes. After a time the mucous membrane is no longer anæmic, but passes into a state of physiological congestion, in striking contrast with the antecedent condition of anæmia. During this state of congestion the cells receive an abundance of oxygen, and the active oxidations which take place probably complete the decompositions that result in the formation of the proënzymes, while the increased amount of fluid in the cells helps to secure the passage of the ferments into the stomach as a part of the gastric juice.

The conditions are different in the case of hydrochloric acid. This active constituent of the gastric juice does not exist in the glandular cells as acid, and before the acid can become a constituent of the gastric juice it is essential to form it anew after the disruption of sodium chloride and the rearrangement of certain chemical affinities. The production and secretion of hydrochloric acid are thus two acts more widely separated in character than the production of pepsinogen or pepsin and the secretion of pepsin.

It seems likely from a consideration of the differences in the processes of pepsin and acid formation and secretion that the secretion of acid involves more complex conditions than those attending the mere secretion of pepsin. If this be so, it is easy to see why the pepsin-secreting function of the stomach is so stable as compared with the acid-secreting function, and why the latter is so readily disturbed by influences which have relatively little effect on the secretion of pepsin.

I told you that there are three essential constituents of

the gastric juice, the hydrochloric acid, the ferments, and the water. The hydrochloric acid and the ferments we have considered sufficiently for our present purpose. The water of the gastric juice must be separately considered because the conditions under which it is secreted are largely independent of those relating to the secretion of acid and of the ferments. The independence of this diluent function of the stomach shows itself clinically in the occurrence of gastric disease in which there is a watery secretion containing neither ferments nor combined acid. In the rare disease called achylia gastrica there is said to be at times a slight secretion of this kind. No gastric digestion occurs under these conditions, and a test breakfast is found to be quite unaltered at the end of one hour or more. The absence of the rennin ferment is shown by the fact that milk remains in the stomach without undergoing coagulation. It is surprising to find how little the general nutrition and health may suffer in persons who secrete only a small amount of gastric fluid containing neither hydrochloric acid nor the ferments. The intestine in these cases appears capable of compensating in large degree the loss of gastric function.

The independence of the diluent function of the gastric mucosa is also shown by physiological experiment. Thus Schneyer found that although irritation of the vagi is commonly followed by the secretion of a gastric juice containing both acid and ferments, it was possible after a period of starvation to obtain a secretion containing neither of these constituents. The action of pilocarpine is also instructive in this connection. There are patients in whom the subcutaneous use of this drug is followed by a very free secretion of a gastric juice which shows an abnormally high water content, a percentage of pepsin only a little below the normal, and a greatly diminished secretion of acid.

From what has been already said it is evident that the cellular activities of the gastric glands are by no means the same in the secretion of the ferments, the hydrochloric acid, and the water of the gastric juice. The functional activity most readily abolished by disease is that relating to the secretion of hydrochloric acid; the ferment-secreting function shows much greater resistance to most of the influences that create gastric disease. Most resistent of all is the diluent function of the stomach which probably involves cellular activities of a less special character than the other

secretions, and which depends more largely upon the simpler physical activities like those concerned with osmosis and filtration.

While it is beside our purpose to discuss the therapeutics of gastric disease in a systematic and detailed manner, I cannot omit some reference to the principles that should guide our efforts in the direction of successful treatment. So far as the derangements of gastric secretion are concerned we have to do with two prognostically different sets of cases, namely, those without and those with disturbances of motility. I wish here to say something about our ability to modify the derangements of gastric secretion, without reference to their association with troubles of motility.

Since the digesting activity of the gastric juice depends on the secretion of hydrochloric acid and on the secretion of ferments, two functions based on very different physiological conditions, it is necessary to consider separately the therapeutics of deranged acid production and ferment production.

We have already seen that the secretion of hydrochloric acid is powerfully influenced by conditions of innervation and by the state of the glandular apparatus. One might therefore hope to modify the secretion of acid, either by way of the nervous system or directly by way of the acid-forming cells of the mucosa. By securing to a patient an out-of-door life, with a judicious combination of physical exercise and rest, we obtain conditions of innervation that strongly favour a re-establishment of the normal secretion of hydrochloric acid. Singular as it may appear, this favourable influence of rest applies both to states of diminished acidity and to hyperchlorhydria. I will not undertake to explain why this is, but will content myself with mentioning the fact.

While in some instances the re-establishment of normal innervation by these simple means suffices in time to bring about a normal secretion of acid, it is usually necessary to make some effort to influence directly the acid-forming cells of the mucosa. Where there is chronic gastritis daily lavage helps to restore the glandular cells to normal activity, perhaps mainly by the removal of masses of slightly digested food which act as mechanical or chemical irritants. It is also possible to influence the acid-forming cells by means of food and by means of drugs, though it must be owned that observers are not in accord in regard to the effects of food and drugs.

It is well established that different food-stuffs act differently on the secretion of gastric juice. Thus, while meat is a powerful stimulant to gastric secretion, milk calls forth the minimal secretory effort necessary for digestion. In a condition of hyperchlorhydria both meat and milk are capable of entering into combination with the free acid, and of reducing in this way the amount of free acid. This leads often to a prompt diminution in painful gastric sensations. The effect is, however, only temporary, for there is soon a production of more acid. Milk is to be preferred to meats, probably because it calls forth a less abundant secretion of acid. It is desirable to use milk rich in cream, because fat has some inhibitory action on the secretion of free hydrochloric acid. In cases where there is gastric atony with hyperchlorhydria it is sometimes important not to give carbohydrates abundantly, because the products of their decomposition may stimulate an excessive secretion of acid. In states accompanied by diminished secretion of free acid it is especially important not to overfeed, since it is easy to allow more proteid than can be converted into the normal acid products of proteid digestion—a condition favourable to excessive putrefaction of food. It is difficult to say whether milk or meat is to be preferred under these circumstances. Milk has the advantage of requiring less secretory effort on the part of the glandular cells to effect digestion; meats, on the other hand, stimulate secretion, and this physiological stimulation is probably desirable. I think it is well to allow a good deal of milk in these cases and a moderate quantity of meat. Remember that the carbohydrates readily ferment where there is little or no free hydrochloric acid, and that they must therefore be allowed with some caution.

Some drugs have a decided effect on the production of acid. Thus atropia exerts a powerful inhibitory effect on the gastric juice, not only in health, but in states of hyperchlorhydria. We can advantageously restrain this action in some instances, but I do not advise you ever to place your main reliance on this drug. Many physicians use the alkalis to neutralise an excess of acid. There is a difference of opinion as to whether the alkalis merely neutralise acid already secreted, or whether they also act on the glandular cells in a specific way. I am inclined to agree with Reichmann that their effect is limited to the neutralisation of acid already secreted. Preparations of magnesia are to

be preferred to the carbonates of the alkalis, because they do not form irritant chlorides.

I consider the alkalis valuable as temporary palliatives, but not for continued medication, as they do not affect the real causes of the excessive secretion of acid.

Although drugs are very extensively employed with a view to increasing the flow of gastric juice, and incidentally the amount of hydrochloric acid, I think we have no satisfactory evidence that there are any medicinal agents that can be relied upon to produce this result. Bitter tonics, ipecac and various salts are still confidently employed to stimulate gastric secretion, but upon insufficient grounds. We have lately been assured that the drug known as orexin increases the secretion of hydrochloric acid, but the observation is one which requires confirmation for cases of gastric disease. There is also no satisfactory proof that electrical applications to the mucosa increase gastric secretion. Weak alcoholic drinks can advantageously be used to stimulate the secretion of gastric juice where the depression of function is due to general causes, such as fever or nervous exhaustion, but not where there is gastritis.

It is, of course, obvious that where there is extensive atrophy of the gastric tubules it is most irrational to give drugs with a view to increasing secretion.

But while we have no drugs at present that will certainly increase the flow of gastric juice, we have a very simple way of making up the deficiency of hydrochloric acid, namely, by the administration of this acid in suitable dilution. From what we know of the physiology of the gastric juice one is justified in believing that the medicinal use of hydrochloric acid is beneficial on account of its bactericidal action, because it helps to convert the proënzymes into ferments, because it saturates proteids with the formation of acid products, because it favours normal gastric peristalsis, and because the free acid stimulates the secretion of pancreatic juice. Many writers of large experience are, however, sceptical in reference to the therapeutics of hydrochloric acid. They point out, among other things, that it necessitates impracticably large amounts of the acid to effect saturation of the proteids, and that smaller doses are probably useless. Thus, according to careful studies made by Fleischer, it requires 0·05 gram of hydrochloric acid to convert 1 gram of egg albumin into acid albumin or syntonin. Assuming that the gastric juice

contains two parts of hydrochloric acid per thousand, it would require 3½ litres of gastric juice to change 150 grams of egg albumin into acid albumin, or 30 grams of a 25 per cent. solution. One hundred drops of the dilute acid, equivalent to 12·5 per cent. of strong acid, is capable of saturating only 15 grams of egg albumin. It is thus clear enough that we can give therapeutically only enough hydrochloric acid to saturate a small quantity of proteid. But the knowledge of these limitations does not justify us in saying that hydrochloric acid is of no therapeutic use. The use of the acid in practicable doses is certainly a help in effecting the digestion of proteids, which, as we know, are only in part digested in the stomach. Clinical indications certainly favour the use of the free acid in cases where there is a marked failure in the secretion of gastric juice. In achlorhydria of neurotic origin I think it unwise to rely indefinitely on the acid, because its use does not improve the real conditions. In cases of achylia gastrica, however, where the gland cells are hopelessly atrophied, there may be considerable benefit from the use of rather large doses of the dilute acid (U.S. Phar.), say twenty drops at the height of each meal and twenty drops half an hour later.

The conditions of rest and exercise which favour the restitution of normal conditions of acid secretion also favour a return of the normal secretion of the ferments of the gastric juice. From what I have said of the greater stability of the ferment-making functions of the stomach as compared with its acid-producing function, one might infer that ferment secretion is not readily influenced by means of drugs. Excessive ferment secretion is an unknown condition, and our therapeutic efforts therefore relate only to cases where the ferment secretion is diminished.

I do not know of any drugs which can be employed therapeutically to increase the secretion of the peptic and milk-curdling ferments. We can, however, introduce ferments with the food which are capable of supplementing the deficiency in the normal ferments. Several different ferments are used for this purpose, among them pepsin, pancreatin, papoid, caroid, and the ferments of the pine-apple.

While pepsin may perhaps be of some service in starting the process of peptonisation where there is free hydro-

chloric acid in the stomach, the fact that an acid medium is necessary for its action greatly limits its utility, since its action is probably checked in the upper intestine. Pancreatin, which acts in alkaline media, is adapted to action in the intestine, but is commonly useless because it is destroyed by the action of free acid in the stomach. It may be used, however, in cases of chronic gastritis with persistent absence both of acid and ferments, and there are experiments which indicate that the process of peptonisation thus initiated in the stomach leads to a better utilisation of proteids than would otherwise be the case. I believe that papoid and caroid, ferments obtained from the milky juice of trees of the family of Papayaceæ, are of much greater practical service than pancreatin, though clinical and experimental observation has not yet definitely established their place in therapeutics. Both papoid and caroid peptonise energetically and have the great advantage of acting well in acid, neutral, and alkaline media.

Although the peptonising ferments are often helpful in forms of gastritis in which the gastric ferments continue to be secreted in considerable amounts, I am opposed to their prolonged use except in cases where there is a persistent absence or great diminution of these ferments, dependent presumably on incurable histological alterations in the glandular structures. I base this view on the belief that where the diminution in the ferments is not dependent on structural disease a sufficient secretion can be re-established by other therapeutic means, and that under these circumstances it is not wise to make a practice of supplying peptonising agents from without.

Although it is important for us as clinicians to take account of the secretory disturbances of the stomach, let us not commit the common error of overestimating their importance and of subordinating all other therapeutics to our efforts at gastric treatment. Let us rather bear in mind all the indications for treatment, considering carefully the intestinal as well as the gastric conditions, and looking well to the general therapeutic indications, for it rarely happens that a secretory disorder of the stomach is the sole indication for treatment. Often such indications, though not without importance, are subordinate to others derived from various associated disturbances, and the gastric treatment must take only its appropriate place in the general therapeutic plans.

Mature judgment and much experience are required to make the most intelligent plan for meeting varied and sometimes antagonistic indications for treatment.

We have discussed briefly some of the leading features relating to alterations in the secretion of the gastric juice. Let me now call your attention to a disorder of gastric secretion characterised by the increased formation of mucus. You know that in health the mucous glands of the stomach secrete a small quantity of mucus, and that in conditions of disease this secretion is frequently much increased. Thus in the course of the various forms of acute gastritis the swelling of the mucous membrane is associated with a diminution in the secretion of the gastric juice, and a marked increase in the secretion of mucus. In the chronic forms of gastritis there are great differences as to the degree of mucus formation. There are certain types of chronic gastritis in which there is very little or no increase whatever in the formation of mucus, and others in which there is a regular and large increase. In the cases where there is a regular and large increase in the secretion of mucus, the condition is so distinctive that it deserves recognition as a distinct type of chronic gastritis, both clinically and pathologically. In the state often called chronic mucous gastritis the gland-cells, especially those in the pyloric region and in the greater curvature, undergo a mucoid degeneration. The protoplasm of many of the gland-cells may be wholly replaced by mucus. Associated with the abundant secretion of mucus there is usually a marked diminution or loss of free hydrochloric acid. Clinically these cases of mucous gastritis are generally characterised by nausea, which often persists a considerable part of the day, and sometimes leads to vomiting. The stomach is unduly sensitive to the presence of food, especially if it be cold or very warm. Some epigastric tenderness is generally present. I have observed that headache, usually frontal, frequently accompanies the nausea, although it occurs at times independently. When the stomach is emptied by lavage or by vomiting there is an abundance of stringy or lumpy mucus. The mucus and the food often have a peculiar pungent odour, due to the presence of butyric acid. As a rule patients with mucous gastritis have committed many indiscretions in diet, both as regards the quantity and quality of their food.

There is one little point relating to these cases of mucous gastritis which I would like you to bear in mind. This is that the mucus secreted by the stomach may find its way into the fæces. I have several times known this to lead to the diagnosis of mucous colitis. You will find that in consequence of washing the stomach carefully the mucus ceases to appear in the movements. We frequently see relapses after years have gone by, and the patient who has once had a typical mucous gastritis almost always develops the same form of disease when a relapse occurs. Sometimes, however, the mucous glands undergo atrophy, and then there is a great diminution in the secretion of mucus.

Let us pass now to a consideration of the disorders of motility observed in the course of gastric disease. These disorders are of two kinds—those in which there is an excess of motility and those in which the motor powers of the stomach are lessened. Cases in which there is excessive motility are much less common than those in which the opposite conditions exist, and they are also of much less significance for the digestive functions. Where the motility of the stomach is exaggerated there is commonly a state of peristaltic unrest in which the patient is more or less distinctly conscious of abnormal activity in the walls of the stomach. The peristalsis as a rule takes the normal direction, that is, towards the pylorus, but in some instances there is a reversal of the normal direction. It is necessary to distinguish between those cases in which the trouble has a neurotic origin, as in hysterical and neurasthenic patients, and those in which there is a structural obstacle to the emptying of the stomach which incites the stomach to undue activity. The cases of functional origin often depend on hyperacidity of the gastric contents, the increase in acidity being due either to an increase in free hydrochloric acid or to an increase in organic acids. In many persons such hyperacidity leads to no excess in the motility of the stomach, and we have to assume the existence of an over-irritable nervous mechanism in those cases where moderate hyperacidity stimulates the stomach to increased peristalsis. It is possible that pyloric cramp is the usual precursor of the increased movement of the stomach as a whole.

Much more important in its consequences to the organism are the disturbances associated with diminished gastric

motility. The diminution in motor function is almost invariably associated with diminished secretion of hydrochloric acid and with some degree of chronic gastritis. After a time the atony of the stomach wall is usually followed by dilatation with its varied consequences. The pathological significance of impaired gastric motility lies in the fact that the diminished activity of the stomach leads to a delay in emptying the stomach. This delay greatly favours fermentative alterations in the retained food, and these fermentative processes carry with them a long train of pathological consequences, including gastritis, impaired nutrition from loss of food potential, and the effects of the absorption of slightly toxic substances arising from the decomposition of food. I may say here that the formation of poisons in the stomach, even in conditions of marked dilatation, is probably not of so much importance as many writers have supposed. Apart from the fatty acids, lactic acid, alcohol, acetone, and sulphuretted hydrogen, there is no evidence that toxic substances are formed.

All conditions which exhaust the nervous system favour the production of atony of the stomach. This is true of exhausting diseases, prolonged worry, excessive mental work, undue sexual excitement, &c. The condition is a common one in neurasthenia and in hysterical patients. Perhaps the first change is a diminished secretion of gastric juice, together with a diminished secretion of hydrochloric acid. It is easy to imagine that the removal of the normal stimulus of the gastric juice should lead to atony, since there is probably a close connection between the nervous activities that lead to the presence of free hydrochloric acid and those stimuli which cause the stomach to empty itself. For a long time a moderate degree of atony may exist without impairing general health. But sooner or later dilatation of the stomach occurs, and this almost always leads to some loss of weight and strength. I think it very probable that the excessive use of food and especially of fluids is frequently a factor in giving rise to dilatation. Although the sequence of events doubtless differs somewhat in different cases, it is likely that most cases of gastric dilatation are brought about through the association of diminished secretion of hydrochloric acid, atony of the stomach wall, and excesses in eating and drinking. A considerable degree of dilatation may arise under these circumstances, but if the pyloric opening is not

narrowed we are not apt to see the extreme grades of gastric dilatation. When the pyloric opening becomes the seat of mechanical obstruction a serious factor is introduced. Under these conditions the dilatation of the stomach may reach an extreme degree. It is very important to recognise the existence of obstruction at the pylorus, for the cases in which this exists differ greatly in prognosis and in treatment from those in which there is a free exit for the food. It is sometimes a difficult matter to determine whether we have to deal with a pyloric stenosis or not. I think the most reliable guide in this connection is to be found in the state of the stomach after the night's rest. If you find that the stomach of a patient who takes a good-sized dinner at seven in the evening contains much food at seven o'clock in the morning, and shows this condition regularly, you can be almost positive that there is some obstruction at the pyloric opening. This criterion is also of much importance in giving an indication as to treatment, for if the stomach fails to empty itself after you have made use of the ordinary therapeutic measures this fact becomes a highly important indication for surgical interference. On the other hand, if your patient with dilatation of the stomach succeeds in emptying the organ during the night it is not likely that there exists an obstruction of sufficient gravity to warrant operative procedure.

It is necessary that you should make a further distinction in cases of dilatation with stenosis at the pylorus. A certain number of these are due to malignant disease at or near the pyloric opening. Perhaps an equally large number of cases of pyloric stenosis are dependent on conditions wholly unconnected with malignant disease. The relative frequency of non-malignant stenosis is a fact which physicians have only recently begun to recognise. If you bear in mind the existence of cases of dilatation of the stomach due to non-malignant stricture of the pylorus from fibrous changes (often secondary to ulcer) or from congenital malformations, you will have the satisfaction every now and then of literally saving the life of some wretched patient by insisting on timely operation.

The symptoms of dilatation of the stomach vary a good deal with the degree of the affection, and especially with the ability of the stomach to get rid of its contents through the pylorus. In the slighter degrees of dilatation, where the

stomach empties itself completely, though slowly, there are various trivial disturbances of digestion, such as nausea, gastric discomfort, flatulence, and perhaps some loss of weight. Where the dilatation is great and the stomach only slowly and imperfectly empties itself, there is a condition of slow starvation attended by gradual loss of weight and strength and symptoms of an exhausted nervous system. In some instances persistent vomiting helps to reduce the strength of the patient. I consider mental depression a very common association of considerable dilatation of the stomach. When well advanced these cases regularly show alterations in the urine referable to slow starvation, to excessive carbohydrate fermentation, and to excessive proteid putrefaction in the intestine. The urinary indications of starvation are a very low output of sodium chloride associated with the excretion of a moderately or considerably diminished quantity of nitrogen, phosphoric and sulphuric acid, a diminished excretion of uric acid, and sometimes the presence of acetone. The quantity of urine is reduced owing to the diminished absorption of water, water being absorbed from the stomach to only a limited extent. In moderate dilatation the volume of the urine is commonly below 1000 c.c. in the twenty-four hours. In extreme dilatation it may fall to 500 c.c. or less. There is also a diminution in the volume of the fæces, as might be expected where so little food passes the pylorus. This diminution is a valuable index to the quantity of food that reaches the intestine. A normal adult passes from 100 to 200 grams of fæces daily, but the quantity may average much less than 60 grams when there is serious pyloric obstruction.

Since excessive intestinal putrefaction is almost always a feature of cases of gastric dilatation, we should expect to find the various symptoms which I have described to you in talking about excessive fermentation and putrefaction. These indirect effects are indeed common in persons with decided dilatation ; but, as already mentioned, it is exceedingly difficult to say with positiveness just which symptoms are referable to the products of excessive putrefaction. We have still much to learn on this subject.

Another pathological association of cases of dilatation is what I have already spoken of as a state of acidosis, or mild acid intoxication, when referring to the chemical defences against disease. In six cases of marked gastric dilatation

which I have studied, the evidences of such a condition have been present as a persistent condition little amenable to treatment. In one of my cases I observed a decrease in the evidences of this intoxication after months of lavage and out-of-door life. The character of the pathological organic acid or acids we do not yet know. We have determined only that the known bases exceed the known acids of the urine, this being, as I have explained, the evidence of an elimination of unknown organic acids. Neither do we know as yet in what relation this condition stands to the symptoms of dilatation. It is possible that the organic acid to which I refer is an acid formed in the stomach owing to fermentation, but at present I think it more likely that the acid is derived from some obscure metabolic disturbance caused by toxic products absorbed from the gastro-enteric tract. The indications of carbohydrate fermentation, as evidenced by the urine, are chiefly the presence of fatty acids in excess. These fatty acids are derived from the decomposition of carbohydrates in the stomach. The signs of excessive intestinal putrefaction are chiefly an increase in the indican of the urine, an increased output of phenol, and a marked change in the ratio of the ethereal sulphates to the preformed sulphates.

A careful physical examination is always essential to the recognition of the various consequences of diminished gastric motility. The degree of dilatation is readily made out by fully inflating the stomach with air. It is better to do this by means of a bulb attached to a stomach tube than through the use of the seidlitz-powder test. The position of the stomach and its size when inflated enable you to distinguish between a lowering of the stomach as a whole, that is, a gastroptosis, and a dilatation of the organ. Examination aids you in distinguishing a distended and misplaced colon from a distended stomach. When you have concluded that there is a considerable dilatation, together with an obstruction at the pylorus, it may be difficult or even impossible to determine with certainty whether you are dealing with a stenosis of benign or malignant origin. There are some points to guide you in the diagnosis. If the patient is under forty, a malignant stenosis is unlikely if the other indications are evenly balanced. If the loss of weight and strength has been very gradual, and if the patient has a history of marked dyspepsia extending back one or more years, the stenosis is

more likely to be non-malignant than malignant. Rapid loss of weight in a person over forty suggests carcinoma, and the presence of much pain and a history of vomiting blood greatly increase this probability. The latter symptoms may, however, be entirely wanting in carcinoma. The occurrence of vomiting of food does not help one, since it is common in both conditions; neither does the presence of lactic acid, which was once thought to be almost distinctive of carcinoma. Considerable amounts of lactic acid are liable to be formed whenever the stomach is greatly dilated from any cause. The presence of free hydrochloric acid in fair amount is rather against carcinoma, but you must remember that we may have even a hyperchlorhydria in cases of carcinoma growing on the base of an old ulcer. If free hydrochloric acid is persistently absent, it is probably a little in favour of carcinoma.

I consider it important for you to be acquainted with the fact that the disorder of secretion which was described by Reichmann as gastro-succorrhœa chronica, and by Riegel as chronic supersecretion, is usually one of the consequences of dilatation of the stomach. This disorder is characterised by the chronic and uninterrupted secretion of gastric juice in the fasting as well as in the food-containing stomach. The gastric juice secreted by the supposedly empty stomach contains both hydrochloric acid and the ferments.

The chronic and continuous flow of gastric juice was originally regarded as a primary disorder, quite independent of demonstrable alterations in the structure of the stomach, and due to some pathological state of the nervous system. That cases of this sort do occasionally occur seems beyond doubt, but it appears to be true that most of the instances of secretory disorder characterised by chronic continuous flow of gastric juice are far from being independent of structural disease, and are, indeed, to be considered secondary to definite lesions of the stomach. Thus there are cases of dilatation of the stomach in which the irritation of retained food or its products is the cause of a chronic continuous flow of gastric juice containing a high percentage of hydrochloric acid. Wash the stomach thoroughly a few hours after each meal, so as to prevent stagnation of food, and you will notice a reduction or complete disappearance of gastric juice during the fasting state. Likewise in gastric ulcer there is often a chronic continuous flow of gastric juice

of high acidity. Even in some apparently normal persons one finds some gastric juice at a time when the stomach is supposed to be resting in its secretory work. Careful examination shows that the organ contains fine particles of food, and that gastric digestion is really in progress. It is certain that in many of the supposedly 'primary' cases of chronic gastro-succorrhœa the stomach is not free from food at the times when it is supposed to be empty. Thus, even in these cases, one may suspect that gastric digestion is really going on in a slight degree when the stomach is thought to be free from food. It is of interest in this connection that in some typical 'primary' cases of chronic gastro-succorrhœa the stomach has ceased to secrete gastric juice before breakfast, after the patient had been subjected to a gastro-enterostomy, or after rectal feeding had been practised for several days.

Although it is true that in most instances of chronic gastro-succorrhœa there is an excessive secretion of hydrochloric acid, there are instances of the condition in which the excessive flow of gastric juice is attended by a marked diminution in free hydrochloric acid. This has been noted, for example, in cancer of the pylorus.

The treatment of simple dilatation of the stomach is usually satisfactory. Patients should be advised to take frequent meals of moderate size, and should be cautioned against overloading the stomach. This precaution as regards diet should be combined with the regular and thorough lavage of the stomach, at least three times a week, until the signs of dilatation are distinctly lessened. It is advantageous to add twenty or thirty minims of nux vomica to the wash water. If with these measures the patient be placed under reasonably favourable conditions as regards exercise, rest, freedom from worry, &c., you will see a rapid change for the better. I think you will frequently be surprised at the quick improvement in local symptoms and in strength and weight. There is, however, always some danger of a relapse into less favourable conditions unless the patient is willing to practise self-denial in reference to the pleasures of the table.

In the cases of dilatation which are dependent on a stenosis, the treatment must frequently be surgical in character. In the cases of malignant disease extirpation of the tumour should be practised if the disease be not too advanced. But even where the disease has extended so

as to make extirpation impracticable operative treatment is often positively indicated. The operation has for its object the establishment of a new outlet from the stomach. Such an outlet, as you know, can be obtained by the operation of gastro-enterostomy.

If you will stop for a moment to reflect on the facts which we have considered in speaking of the secretory and motor derangements of the stomach, you will observe how close is the relation between the two kinds of disorders. While it is true that secretory derangements may exist independently of alterations in the functions of motility, there is no doubt that the former usually favour the development of the latter. The commonest type of digestive disorder, slight chronic gastritis with diminution in the secretion of free hydrochloric acid, usually soon leads to some degree of gastric atony, and this gastric atony is often the precursor of dilatation, slight or considerable. You will also have observed that the establishment of a disorder of motility promotes the continuance of secretory disturbance. This is especially noticeable in cases of dilatation, in which the stagnation of food permits the formation of products of fermentation, which in turn have an influence on the secretion of hydrochloric acid. The gastritis set up by these irritant products usually has the effect of still further checking the secretion of hydrochloric acid, but in some instances, owing doubtless to idiosyncrasies of innervation, these products excite the opposite condition, namely, an excessive secretion of acid. Indeed, there are instances in which, owing to conditions still unknown, a state of achlorhydria or hypochlorhydria is quickly followed by a temporary excess of free hydrochloric acid in the gastric juice.

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LECTURE IX

THE CHEMICAL PATHOLOGY OF INTESTINAL DIGESTION

Importance of intestinal digestion—Derangements of intestinal secretion; of motility—Characters of the bile—Resorption from the gall-bladder; from the intestine—Functions of the bile—Emulsification of fats—Effect on fat absorption of excluding the bile—Effect of bile on peristalsis—Supposed antiseptic action—Experiments of Pawlow showing effect of bile on action of pancreatic ferments—Influence of exclusion of bile in the human subject—Influence of bile on certain purgatives—Causes of diminished biliary secretion—Characters of the pancreatic juice—Amylolytic, steaptic, and proteolytic ferments—Effects of diminished pancreatic secretion—Causes—Effects of diminished biliary and pancreatic secretion—Changes in the urine caused by disorders of intestinal digestion—Increased excretion of uric acid—Increased excretion of other organic acids—Excess of ethereal sulphates—Treatment of disorders attended with diminished secretion of bile and pancreatic juice—Cholagogue drugs—Ox-bile—Effect of pancreatic gland on fat absorption—Rest and diet in acute duodenitis—Diet in chronic duodenitis—The succus entericus—A 'ferment of ferments'—Effects o diminished secretion of the succus entericus—Increased secretion of intestinal mucus—Mucous colitis—Disorders of intestinal motility—Increased motility: colic, diarrhœa—Green stools—'Fat diarrhœa'—Constipation—Its effects—Increased intestinal putrefaction—Increase of urobilin of the urine from increased absorption—Elements in treatment of diarrhœa and constipation—Rectal alimentation.

We pass this morning to the disorders of intestinal digestion. While the pathological chemistry of gastric digestion has been more carefully studied than that of intestinal digestion, owing largely to the facility in obtaining the gastric contents for study, it is likely that knowledge of the pathology of intestinal digestion is even more essential to an understanding of the diseases of nutrition. There is no doubt that intestinal digestion has a much more important *rôle* in carrying on the nutrition of the body than has digestion in the stomach. It is possible for dogs, and even for human beings, to live and maintain a good state of nutrition for

considerable periods of time after total extirpation of the stomach; but we cannot conceive that nutritive functions sufficient for the maintenance of life could be carried on after the complete elimination of the functions of the small intestine, although nutrition may not be appreciably impaired after removal of two or three feet of the intestine. I shall speak to you to-day, from the standpoint of pathological chemistry, of certain disorders of secretion and of motility that occur in the course of intestinal disorders. The disorders of secretion include the diminished secretion of the bile, of the pancreatic juice, and of the succus entericus, and the increased secretion of mucus. The disorders of motility comprise excessive peristaltic activity and diminished peristaltic activity.

The disorders of intestinal secretion are common and important. I shall begin my sketch of these disturbances by reviewing with you some of the more important facts connected with the diminished secretion of the bile, after reminding you of the chief characters of this secretion. You will remember that the bile in the gall-bladder is an alkaline golden-yellow or brown fluid, sometimes possessing a greenish tint. The bile has a bitter taste with a sweet after-taste. Its specific gravity varies from 1·010 to 1·040. In health there are probably considerable variations as to the quantity formed in twenty-four hours. Probably from 400 to 600 c.c. are daily discharged in the intestine of an adult under ordinary conditions, but the amount may fall as low as 300 c.c. or reach 1,000 c.c. The bile contains from one to two per cent. of the bile-acids. These, as you remember, are combinations of cholic acid with glycocoll and taurin, forming respectively glycocholic and taurocholic acid. The bile-acids hold in solution considerable quantities of cholesterin and lecithin, an important function, of which I shall say more in another connection. The colour of human bile is due largely to bilirubin, a derivative of hæmoglobin. Other bile-pigments are present, but they need not be specially mentioned. Besides these chief constituents of the bile, it contains a small quantity of soaps, fats, and urea, and a variable quantity of mucin. The inorganic salts of the bile are chlorides and phosphates. A little iron and perhaps a trace of copper are normal constituents. The bile contains a small percentage of oxygen and a large percentage of carbon dioxide. What we know of human bile is the result of observations on fistulæ, and we cannot

assume that the conditions of secretion are here wholly normal.

The bile in the gall-bladder undergoes a resorption of some of its constituents. This resorption relates especially to water, to iron, and the bile-salts. A resorption of the bile-salts also goes on from the intestine, so that we may look upon these salts as being preserved for use in the organism instead of being discarded like excretory products.

The bile must be regarded as being in part a secretion useful to digestion, but also as an excretion which gets rid of various known and unknown materials, including living and dead bacteria, the *débris* of red blood cells, &c.

The functions of the bile in the intestine are of at least three sorts. First, its presence favours the absorption of fats. This property it owes partly to an emulsifying action on the part of the cholates or bile-salts, which also have the power of dissolving otherwise insoluble soaps of calcium and magnesium. The emulsion formed through the action of the bile promotes the formation of soaps, which, as I have already pointed out to you, are readily absorbed from the intestine. The bile-salts probably play an important part in bringing about the formation of soaps. The importance of the bile for the absorption of fats can be shown in the case of the dog by a very simple experiment. Thus a normal dog of large size fed on 150 to 250 grams of fat daily absorbs from 75 per cent. to 90 per cent. of this amount. If now a fistula be formed so that the bile is diverted from the intestine, much the greater part of the fat is lost in the fæces, even if the total amount of fat given be reduced to 100 or 150 grams. A second function of the bile is that of stimulating intestinal peristalsis. This is shown by the constipation which follows the experimental diversion of the bile from the intestine. The purgative action of the bile is referred by Stadelmann to the irritant action of the bile-salts on the colon. The third function of the bile is its antiseptic action, an action which has been much overrated The influence of bile on putrefactive bacteria is only slight, and is quickly lost on exposure to the action of such micro-organisms. It is even claimed that sterile bile undergoes decomposition on keeping. Nevertheless the bile exerts indirectly an important effect in keeping the putrefactive processes in the intestine within normal limits. This it does partly by stimulating peristaltic action and hurrying onwards

the food through the intestine. It also acts indirectly on putrefaction by its effect on fat absorption, since the presence of large amounts of fat in the intestine is favourable to putrefactive decomposition. Quite recently a further function of the bile has been discovered—namely, that of dissolving very readily certain specific bacteria of a pathogenic character.

Experimental observations by Pawlow and his pupils promise to throw new light on the nature of the functions of the bile, at least so far as the dog is concerned. These observations indicate that the bile has little chemical action on the various food-stuffs, but that it has the very important property of reinforcing the ferment action of the pancreatic juice. This auxiliary activity of the bile was found to be especially marked in reference to the fat-splitting ferment of the pancreas, but the action on the proteolytic and amylolytic ferments, though less pronounced, was also marked. Perhaps in man the diminution in fat absorption following exclusion of the bile is due in part to the withdrawal of this reinforcing action of the bile on the pancreatic juice, which might impair the fat-splitting function. Where the fat ingested is in moderate amount one would not expect a noticeable falling off in fat absorption.

Experiments conducted on dogs, in which the dislocated duodenal papilla, with a bit of the adjacent mucous membrane, was kept under observation, showed that no bile is secreted in the starving state. Moreover water, acids, uncooked albumin, and cooked starch failed to excite any secretion. On the other hand, fat, the extractives of meats, and the products of proteid digestion gave rise to a free flow of bile. It thus appears that the bile-flow is excited by specific stimuli. There is also a close correspondence in time between the rise and fall of the biliary secretion and the pancreatic juice—a fact in itself strongly suggestive of the close physiological relation between the two secretions.

The bile strongly retards the action of the peptic ferment, and there can be little doubt that the concentration of the bile during digestion is sufficient to put an end to the peptic digestion of proteids. This action of the bile on pepsin, a ferment injurious to the action of the pancreatic ferments, taken in conjunction with the helpful effect of the bile on the pancreatic ferments, leads one to believe that an important function of the bile is to facilitate the transition from gastric to duodenal digestion.

From what I have told you of the functions of the bile you can deduce for yourselves the nature of the chief disturbances that follow a diminished secretion of the bile in the human subject. Thus perhaps the most important effect of this diminution is the impaired absorption of fats. Where the pancreatic juice continues to be freely secreted in the human subject the diminution in fat absorption is usually not very great unless the quantity of fat ingested be large; that is, from 200 to 300 grams daily. Indeed, there is reason to think that in exceptional instances there is no diminution whatever in fat absorption, since the pancreatic juice is sometimes capable of compensating for the absence of the bile. On the other hand Müller found from 55·5 to 78·5 per cent. of the ingested fat in the stools of patients with jaundice, where the bile was excluded from the gut without interference with the pancreatic juice. In one of my cases 46·76 per cent. of the food fat reappeared in the fæces. In health the loss probably seldom exceeds 20 per cent., where the fat ingested is not exceptionally large. It is thus apparent that the influence on fat absorption of shutting off the secretion of bile is variable, and considerably less pronounced and less constant in the case of the human subject than in dogs. Whether the digestion and absorption of proteids and starches usually suffer in the human subject through failure of the adjuvant action of the bile is uncertain. But we do know that there are cases of long-standing biliary fistulæ in the human subject in which the general nutrition has not suffered. It cannot, therefore, be held that the presence of bile in the intestine is always essential to the maintenance of health.

Another effect of diminished secretion of bile is constipation, but at times this consequence is not noticeable. The stools are usually offensive where the bile does not enter the intestine. This is probably owing to the increased proteid putrefaction that occurs in the intestine, and of which I have already spoken. The stools are almost always clay-coloured or grey when the bile colouring-matters are excluded from the intestine. You should remember, however, that the presence of clay-coloured stools is not in itself an indication that the bile is shut off wholly. I believe it sometimes happens that the bacterial activity in the intestine leads to a destruction of the bile-pigments or the fæcal pigment urobilin, and hence to clay-coloured stools, even when

a considerable amount of bile is secreted. On the other hand, if the fæces present the normal brown coloration, this is regarded as satisfactory evidence that bile is being freely passed into the intestine. These effects of the diminished secretion of bile are apt to be associated with various symptoms and indications of catarrhal inflammation in the upper part of the small intestine.

There is reason to think that the bile exerts a solvent action on certain drugs of a purgative nature, and that these drugs lose their purgative properties, wholly or partially, when the bile is shut off from the intestine. Thus Buchheim and Stadelmann observed that podophyllum, resin of jalap, resin of scammony, rhubarb, convolvulin, and cathartic acid were largely or wholly robbed of their purgative action when the bile was diverted from the gut.

A diminished secretion of bile may be the result of mechanical causes which hinder the flow of the secretion into the duodenum, or it may result from conditions that occasion a diminished formation of the bile. Among the most important mechanical causes of diminished biliary secretion is inflammation of the duodenal mucous membrane, either acute or chronic. Such inflammation diminishes the size of the opening of the common bile-duct, and may wholly obstruct it. Under these circumstances there is likewise a diminished secretion of pancreatic juice. Gall-stones and the inflammations with which they are associated are also frequent causes of narrowing of the cystic or common duct, or of both. Another important cause of the diminished flow of bile is an alteration in the consistence of the bile, which may become so viscid that it stagnates in the smaller and larger biliary ducts. This sort of obstruction is liable to occur where large numbers of red blood-cells go rapidly to destruction, as in some kinds of jaundice. The conditions that lead to diminished formation of the bile are not well understood, but it is likely that causes leading to depression of the nervous system are capable of diminishing its production. Prominent among such causes are great physical or mental fatigue, worry, sexual excitement, &c. It is likely that the mechanical causes of deficient biliary secretion are frequently combined with causes which act through the nervous system. This is perhaps the case in many instances of slight gastro-duodenal catarrh.

You are, of course, well aware that when the bile is shut

off completely, or almost entirely, from the intestine jaundice soon develops. It is not my intention, however, to speak to you to-day of the influence on the organism at large of obstruction to the bile-flow. This subject is of such importance that I shall have to discuss it with you in a lecture devoted to the purpose.

Let us now consider the effects on digestion that arise from decreased secretion of the pancreatic juice. The pancreatic juice is by far the most important of all the digestive fluids. The pancreas is present in all air-breathing animals, and usually has some representative in organisms lower in the scale of development. The properties of the pancreatic juice have been especially studied in dogs with the aid of experimental fistulæ. It is only occasionally that the opportunity arises in a human being to study the pancreatic secretion, as, for instance, after the removal of a pancreatic cyst. But you can see that the conditions under which one would be likely to have a chance to study the human pancreatic fluid are very apt to be abnormal in character, and hence we really know little of the nature of normal pancreatic juice. In dogs the secretion has a specific gravity of about 1·030 when taken from new-made fistulæ. The fluid is clear, strongly alkaline, and contains from 2 to 15 per cent. of solids. Coagulable proteids are present in variable but often considerable quantity, and may cause the pancreatic juice to solidify on heating, much like the white of egg. The pancreatic juice from recent canine fistulæ coagulates spontaneously. The secretion contains sodium carbonate, and liberates carbon dioxide upon the addition of acid. It contains also alkaline chlorides and a little calcium and magnesium phosphate. The secretion decomposes readily on exposure to putrefactive bacteria, and develops intestinal gases. It contains a little leucin, a little fat, and a small amount of soaps. The pancreatic juice owes its digestive activity to the presence of at least three distinct ferments : a fat-splitting ferment, a starch-converting ferment, and a peptonising ferment. These ferments are known respectively as steapsin, amylopsin, and trypsin. The extracts of pancreas known as pancreatin contain all three ferments.

The amount of pancreatic juice normally secreted by an adult human being probably varies widely even in the same individual. The usual quantity is supposed to be from 200 to 500 c.c. in twenty-four hours. The maximum secretion

in dogs occurs during the first three hours after a meal. Then there is a gradual fall, which reaches the lowest point between the fifth and seventh hour. After this there is a rise, which reaches its maximum from the ninth to the eleventh hour. Unless further food be given the secretion stops between the eighteenth and twenty-fourth hour.

Recent experiments on dogs indicate that the hydrochloric acid of the gastric juice on entering the duodenum with the chyme acts as a powerful physiological stimulus to the secretion of pancreatic juice. It is thought to act in a reflex manner by stimulating the mucous membrane of the duodenum, and it is said that the neutralisation of the hydrochloric acid of the stomach by means of alkalis gives rise to marked diminution in the flow of pancreatic juice. There is some reason to think that the utility of free hydrochloric acid as a therapeutic agent in cases of diminished hydrochloric acid secretion is referable to this action on the pancreatic juice. Fat is another powerful excitant of pancreatic secretion, and the digestibility of milk has been ascribed in part to the readiness with which its fat content excites the flow of pancreatic juice.

The disturbances that attend a decreased secretion of pancreatic juice may be inferred from a knowledge of the functions of the pancreatic secretion. The starch-splitting or amylolytic ferment converts starch partly into dextrin, but chiefly into isomaltose and maltose. Very little glucose is formed. During the first month of life it is thought that no amylopsin is formed, and hence that it is improper to give children starches during this period. A reduction or failure of the amylolytic ferment leads, as one might expect, to impaired digestion of starchy food. As the starch is converted slowly into maltose, it is acted on by bacteria with the formation of carbon dioxide, alcohol, acetic acid, &c. Hence there results a loss of carbohydrate assimilation. The loss of caloric potential of the food leads to loss of weight and to an inability to accumulate fat. Many dyspeptic patients continue very thin in spite of eating carbohydrates in abundance. This is probably owing partly to the impaired conversion and absorption of starchy food. The accumulation of carbon dioxide and other gases occasions flatulence. The fæces show the indications of excessive fermentation, indications to which I have already referred at sufficient

length. In many instances the failure of carbohydrate digestion in the intestine is associated with drowsiness after meals, with slight headache, and with various minor disturbances of well-being. These are perhaps owing in some degree to the absorption of alcohol and various organic acids.

The steaptic or fat-splitting ferment decomposes the neutral fats into fatty acids and glycerine. It also exerts an emulsifying action on the fats, an activity in which it is reinforced by the bile to a considerable extent. One part of the fatty acids set free by the fat-splitting ferment combines with alkalis in the intestine with the formation of soaps. This soap-making process is thought to favour the emulsification of neutral fats. Another portion of the fatty acids is absorbed as such, and probably combines with glycerine in the intestinal wall, again to form neutral fat. As might be anticipated, a reduction or failure of the fat-splitting ferment is followed by defective splitting and absorption of fat. Abelman and Minkowski found a great reduction in the absorption of fat after extirpation of the pancreas in dogs, even when the bile secretion was undisturbed. There are clinical reasons for believing that the effect on fat absorption of shutting off the pancreatic juice is somewhat greater in the case of dogs than in the human subject.

The failure of the steapsin secretion leads to diminished decomposition and absorption of fat, which is frequently shown by the increase in the neutral fat in the fæces. It often happens, however, that, in spite of the steapsin being withheld from the intestine, the neutral fat is decomposed nearly as fully as in health. This is owing to the activity of fat-splitting bacteria in the intestine.

The fat-splitting action of the steapsin is most pronounced in a neutral or alkaline medium. In an acid medium the fat-splitting process is impaired or wholly checked. Hence it is important that we should diet our patients so as to avoid the presence of unnecessary organic acids in the upper part of the intestine, where there is evidence of excessive amounts of neutral fat in the fæces due to diminished fat-splitting.

The third ferment of the pancreatic juice is the one which exerts a proteolytic or proteid-splitting action. It acts well in neutral or slightly alkaline media. Its action is, however, checked by the presence of free acids. As already mentioned, free hydrochloric acid stimulates the pancreatic secretion

and probably does not inhibit the proteolytic ferment because it is quickly neutralised. The action of trypsin on proteids yields albumoses and peptones. These bodies are absorbed as such, but probably become converted into serum albumin in the manner described to you in a previous lecture. Other products of tryptic digestion are leucin, tyrosin, aspartic acid, lysin, and ammonia. Still another product is the body known as tryptophan or protein chromogen, which has been supposed to contribute to the production of the colouring matter of the blood and other pigments.

It is not quite clear whether ammonia is formed chiefly in the intestine or in the intestinal wall. During a meal, and especially during a meal rich in meat, the quantity of ammonia in the tissues of the intestinal wall and in the blood passing from the intestine to the portal vein is very large. This ammonia, on being carried into the liver, is promptly converted into urea.

If tryptic digestion be permitted to run its full course, there is a formation of phenol, indol, skatol, &c. In conditions of normal tryptic digestion these bodies are formed only in small amount, because the albumoses and peptones are promptly absorbed. In conditions where the tryptic digestion is delayed or absorption is slow the aromatic bodies are produced in excess through the proteolytic action of bacteria. In consequence of their formation in the intestine these putrefactive bodies ultimately appear in the urine in conjugation with sulphuric and perhaps other acids, and, as already explained, constitute the chemical indications of excessive intestinal putrefaction.

When tryptic digestion becomes greatly impaired, or altogether ceases, the digestion of proteids is of course markedly diminished. In consequence of this an excessive quantity of nitrogen, representing partly digested or undigested proteid food, finds its way into the fæces. If the quantity of proteid food ingested be only sufficient to maintain the nitrogenous balance of the body in a state of health, and on an ordinary diet, it is easy to see how a loss in nitrogen through the fæces must lead to a loss in the weight of the patient. Such a loss, if large and long continued, gives to metabolic processes the characters that belong to a state of partial and chronic inanition.

In cases where tryptic digestion is much impaired the use of meat in normal amounts is followed by the reappearance

of meat fibre in abundance in the fæces, and microscopical examination will indicate to you the failure in pancreatic digestion. Similarly when the trypsin secretion is diminished or checked the casein of milk appears in the fæces in the form of larger and smaller coagula.

Moderately diminished tryptic secretion presumably leads to some impairment in the nutrition of the body, and is probably a frequent factor in causing loss of weight in persons with intestinal indigestion. Perhaps in many instances the difficulty lies in a moderate reduction in the total amount of pancreatic juice.

I should not wish to give you the idea that proteid digestion cannot be carried on without the aid of the pancreatic ferment. It is certain that the stomach is capable of initiating proteolytic changes of great value in furthering the absorption of albumoses, but there is no reason to suppose that the stomach is ever capable of compensating wholly for a loss of pancreatic digestion. I believe that the persistent exclusion of the pancreatic juice from the gut always leads to starvation.

It seems likely that in disease all three of the chief pancreatic ferments, the fat-splitting, the starch-converting, and the proteolytic, ordinarily suffer diminution together. But there is reason to think that the different ferments are not always diminished in an equal degree. Thus it is said that in fever the ability to digest starches and fat may be much more impaired than the capacity of the pancreatic juice to act on proteids—an observation only to be explained on the assumption that trypsin is, under these circumstances, more abundantly secreted than the other ferments. There is also reason to think that the quantity of the different ferments is determined by the character of the different kinds of food employed, meat calling forth especially the secretion of trypsin, fat the secretion of steapsin, &c.

There has recently been described a fourth pancreatic ferment capable of splitting milk sugar into galactose and dextrose. This ferment appears to be quite distinct from the others, and is secreted only under the stimulus of lactose.

I shall now mention the chief conditions capable of giving rise to a diminished secretion of pancreatic juice. You are probably familiar with most of them, but it will do no harm for me to bring them once more to your attention. Of the conditions which cause a complete and permanent obstruction

of the pancreatic duct the most important is pressure by tumours, from stones, &c. These conditions are, however, relatively rare. Temporary complete checking of the pancreatic secretion or persistent chronic diminution in secretion may result from fever, from states of anæmia, and from prostrating illnesses generally. Most febrile conditions occasion diminished pancreatic secretion. Influences causing extreme nervous exhaustion seem capable of impairing the secretion of pancreatic juice. This is probably true of fright, great grief, mental overwork, worry, and excessive muscular or sexual fatigue. Any acute or chronic inflammation of the duodenal mucous membrane gives rise to similar secretory impairment. States of gastritis usually coexist. Where the pancreas is atrophied we often meet with impaired absorption of fat. Such atrophy, if marked, is sometimes associated with diabetes.

Where there is a diminution in both pancreatic and biliary secretion we get the combined effects of the individual types of disturbance already mentioned. Thus we have loss of flesh and strength, stools containing an excess of neutral fat or fatty acids, or both, an excess of proteids in the fæces, excessive carbohydrate fermentation, and excessive intestinal putrefaction of proteids. I cannot too strongly state my belief that one not rarely meets with these combined disturbances, in moderate degree, where there is presumably no gross structural disease of the pancreas or liver or of their ducts. These disturbances occur in persons with chronic intestinal indigestion, and probably arise in part from impaired innervation and in part from chronic catarrhal gastro-duodenitis. These chronic inflammations, involving the duodenum, appear to me to be the cause of some instances of marasmus or inanition both in children and adults. The pathological conditions in these cases are not yet fully understood.

Since the exclusion of either the bile or the pancreatic juice is capable of causing diminished fat absorption, the mere presence of steatorrhœa does not enable us to distinguish between impaired access of bile and pancreatic juice to the intestine. The presence of jaundice points to exclusion of the bile, but, of course, throws no light on the state of pancreatic secretion. While the presence of an increased amount of fatty acids in the fæces does not help us to distinguish between diminished biliary and pancreatic secretion,

the presence in the fæces of an excessive amount of neutral fat with diminished fatty acids points very strongly to defect in pancreatic secretion. On the other hand, the indication of a normal amount of fatty acids does not exclude pancreatic disease. The suspicion of impaired pancreatic function is further strengthened by the detection of diminished absorption of the products of proteid digestion, for this is not one of the effects of exclusion of the bile.

A further difference between the effects of exclusion of the bile and exclusion of the pancreatic juice is seen in the influence of the administration of raw pancreatic gland. I think there is no doubt that the use of pancreatic gland improves greatly the absorption of fat where the pancreatic secretion is deficient, and that it does not have this effect where the defective absorption of fat depends on exclusion of the bile.

Disturbances of intestinal digestion are capable of bringing about pathological conditions of the urine. Thus they frequently occasion an increased excretion of uric acid, which instead of being excreted, as in health, in about the proportion of one part of uric acid and fifty of urea, may be eliminated in a proportion nearly twice as great. This increase in the uric acid output seems to be closely related to the excessive putrefaction that goes on in the intestine. The nitrogen of ammonia is distinctly increased in some of these patients. As I explained to you in my first lecture, an increase in the nitrogen of ammonia is an indication of the existence of an acid intoxication. I mean by this that the ammonia is excreted in an increased amount in order to neutralise some organic acid which, being incompletely burned, is excreted in excess. That this is actually the case can be shown in many instances of chronic intestinal indigestion by balancing the acids and bases of the urine in the manner which I described to you at the end of the first lecture. The full significance of these slight but chronic states of acid intoxication is not yet clear to us.

I have already brought to your notice the fact that a reduced secretion of bile or a reduced secretion of pancreatic juice is followed by an impaired digestion of proteids, and consequently by excessive intestinal putrefaction and an increased excretion of the ethereal sulphates by the urine. When both the bile and pancreatic juice are completely excluded from the intestine, the ethereal sulphates are

always very largely increased, the proportion of ethereal to the preformed sulphates rising to 1–6 or 1–4, or even 1–1. The indican is likewise much increased.

The question might be asked whether the increased putrefaction in the intestine is not dependent on diminished absorption of albumoses and peptones (with the consequent opportunity for putrefactive decomposition), rather than on diminished secretion of bile and pancreatic juice. It is very difficult to separate the effects of diminished secretion from those of diminished absorption, because the former leads to the latter, and because the conditions which cause diminished absorption usually operate to cause a diminished flow of the digestive juices. I am disposed to believe that such diminished secretion is the chief cause of diminished absorption, except where there is diarrhœa, and that diminished or slowed absorption of proteids without impaired secretion of the bile or pancreatic juice is a very exceptional occurrence.

One of the remote effects of an obstruction to the outlet of the bile is the disappearance of the urobilin of the urine. The urobilin of the urine is apparently identical with the urobilin of the fæces, from which it is derived. But the fæcal urobilin originates from the bile-pigments in the intestine, as I shall explain more fully at our next meeting. Hence it is that diminished secretion of bile occasions diminished urobilin in the urine, or leads to its entire disappearance.

It sometimes happens that bile is regurgitated into the stomach. I have noticed this in persons suffering from dilatation of the stomach, and occasionally in women at the end of pregnancy. The regurgitation is apt to be associated with nausea and indications of chronic gastrititis. It is during the morning hours before breakfast that I have usually noticed the bile in the stomach, and I have been disposed to attribute its presence to continued secretion of bile owing to stagnation of food in the stomach and duodenum.

I desire now to speak to you about some of the elements that enter into the treatment of disorders characterised by a diminished secretion of bile and pancreatic juice. It is obvious that the nature of the therapeutic measures must vary greatly according to the causes of the impaired secretion. Of the surgical conditions I shall not speak to you except to say in passing that the mechanical causes of obstruction to the pancreatic and biliary ducts are much more common than was formerly supposed, and that a

thorough study of the indications for surgical interference will amply repay you.

In medical conditions attended by impaired secretion of bile or pancreatic juice it has long been customary to make use of drugs designed to stimulate secretion, especially the secretion of bile. Very many drugs have been thought to possess a cholagogue, or bile-stimulating action. Among the substances commonly supposed to have a cholagogue influence are calomel, rhubarb, podophyllum, sodium carbonate, turpentine, and sodium salicylate. While the results of experiment are somewhat conflicting, there is no doubt that most of these substances, including calomel, have little effect in stimulating the bile-flow or increasing the solid constituents, and that, on the contrary, many of them seem rather to diminish the flow of bile. The bile-salts when taken by mouth unquestionably increase the secretion of bile. This has been shown, not merely by experiments upon dogs, but also by means of very carefully conducted observations on human subjects with biliary fistulæ. The use of bile-salts or of dried bile has been found to produce both a large increase in the quantity of bile secreted and an increase in the percentage of solids in the bile. Moreover the bile-residue contains a much higher percentage of the bile-salts than is observed in health. In one instance recorded by Pfaff the characteristic salts in the bile-residue were nearly double in percentage while the patient was under treatment with dried ox-bile. The quantity of bile required to distinctly stimulate the human biliary secretion appears not to be large. One quarter of one gramme of dried ox-bile is efficacious, and can be made up into a pill of convenient size. It is desirable to employ a coating which will prevent the liberation of the bile in the stomach: for this purpose a coating of salol has been found useful. Two pills of the size mentioned given three times a day can be counted upon to increase the flow of bile distinctly.

The rational indications for the use of ox-bile as a cholagogue are not yet clearly determined. It would seem to be desirable to avoid the use of cholagogues, especially if, like the bile-salts, they increase the formation of bile in all cases where there is nearly complete obstruction to the passage of bile into the intestine, even if this be due to a catarrhal inflammation. In cases where the bile is present in the fæces, but in diminished amounts, we may safely try the use

of inspissated ox-bile in the hope that it will aid in the absorption of fats by stimulating a greater secretion of bile. It has been shown experimentally that an increase in the quantity of bile poured into the intestine may be followed by a diminution in the size of the stools, owing probably to a diminution in the fats which they contain; a diminution which doubtless corresponds to improved fat absorption. I am not sure that the bile-salts contained in dried ox-bile may not act to some extent directly upon fat through their own presence in the intestine, rather than by stimulating the flow of bile. That they do, however, stimulate the flow of bile in many instances appears probable, because we find both a relief from constipation and a darker coloration of the fæces after the bile-salts have been administered. The determination of the precise conditions in which ox-gall taken by mouth possesses a therapeutic value is well worthy of careful study.

Little is known at present about the possibility of stimulating the flow of pancreatic juice. It is known that pilocarpin increases both the salivary and the pancreatic secretion. The use of pilocarpin is, however, highly objectionable on many accounts, and I question whether we are likely ever to employ it with success as a means of increasing the flow of pancreatic juice. You will remember that I have already referred to the circumstance that the use of fat favours the formation and secretion of pancreatic juice, and, furthermore, that the pancreas is powerfully stimulated to secretory activity through the use of hydrochloric acid. We can utilise these facts in the treatment of conditions where the pancreatic secretion is believed to be reduced but not wholly checked. It is interesting to think that the same conditions which favour the normal secretion of free hydrochloric acid in the stomach at the same time indirectly promote an increased pancreatic secretion.

In another connection I have referred to the influence of the ingestion of raw pancreas upon fat absorption where there is a deficiency in pancreatic secretion. While we do not at present know either the full extent of the usefulness or the limitations of this therapeutic aid, it is certainly a rational and efficient method of compensating in certain respects the defect in pancreatic secretion. Thus in a case of steatorrhœa studied by Von Noorden the patient received from 200 to 250 grams of fat per diem, and the average loss of fat by the stools was 159 grams daily without

treatment, whereas it fell to 39 grams under the use of 125 grams of fresh pancreatic gland. Similar results have been recently obtained by Masuyama and Schied.

Acute or chronic catarrhal inflammation in the duodenum is the usual cause of impaired secretion of bile and pancreatic juice. These processes are usually part of a more general enteritis which is often combined with gastritis or colitis. In acute inflammations involving the duodenum it is of the utmost importance to give the intestine rest for two or three days, just as we give the stomach rest when there is an acute gastritis. We rest the intestine by giving only very small quantities of food of a kind readily digested, up to a certain stage, in the stomach. A fluid diet consisting of peptonised milk, or beef juice, or egg-water, may be employed for this purpose. After a day or two finely chopped underdone beef may be permitted. In severe cases starches and fats should be most carefully avoided for at least two or three days. If there is an inclination to constipation the bowels must be kept open by the use of small doses of calomel, say one-eighth grain every hour until three or four doses have been taken in the day. Unpleasant sensations, and even pain referred to the abdomen, may often be relieved by the use of calomel under these conditions.

The chronic catarrhal inflammations of the intestine, characterised by diminished secretion of bile and pancreatic juice, are often most difficult to treat, and frequently demand much judgment and tact. It is impossible for me to give you detailed instructions, since the treatment of these troubles must be especially adapted to individual cases.

I wish now to remind you of some features of a diminution in the secretion of succus entericus. The succus entericus, or intestinal juice, is formed by the glands of Lieberkühn and Brunner. You know that the Lieberkühn glands are distributed throughout the large and small intestines, whereas those of Brunner are confined to the upper part of the small intestine. The secretion which they produce is colourless, strongly alkaline, and contains a little albumen, together with about 0·9 per cent. of inorganic salts, chiefly sodium carbonate.

The succus entericus acting by itself has very little digestive action. It apparently does not exert any influence of a direct nature upon the proteids and fats. It acts feebly

on cooked starch, and causes some inversion of the sugars known as saccharoses. Notwithstanding this feeble digestive action of the succus entericus, the secretion is probably of much physiological importance. Through the alkaline salts which it contains it promotes proteolysis in the intestine. It moreover affords fluid, and this has the important effect of preventing too dense a consistence of the fæcal material. Thus it distinctly favours the peristaltic action, and is a factor in securing regular movements of the bowels.

But these direct influences of the succus entericus are probably less significant for intestinal digestion than its indirect effect upon digestion through the action which it exerts upon the efficacy of the pancreatic ferments. Experiments made in Pawlow's laboratory indicate that the succus entericus contains a ferment capable of energetically reinforcing the proteolytic ferment of the pancreatic juice, much as the bile reinforces the fat-splitting ferment. This action is exerted most strongly by the secretion derived from the duodenal glands. This is, however, not the full extent of the indirect action of the succus entericus, for this secretion has a not inconsiderable power to aid the amylolytic and fat-splitting ferments of the pancreatic juice. This auxiliary action pertains to the secretion of the entire small intestine. The ferment of the succus entericus may thus be regarded as 'a ferment of ferments.'

The quantity of succus entericus that is daily secreted by the human subject is not definitely known, but is probably large. It has been estimated as amounting to two or three thousand cubic centimetres, that is, considerably more than the secretion of urine during the same period. The secretion of succus entericus begins gradually on the entry of food into the intestine, and is probably continuous in normal persons in that part of the intestine in which the food lies. The little information that we have about the secretion has been obtained by animal experiments in which loops of the intestine have been isolated. The secretion has also been studied in the human intestine after the operation of herniotomy.

A diminished secretion of the succus entericus is a feature in many acute and chronic inflammations of the small intestine. The catarrhal condition doubtless acts in part mechanically by causing a diminution in the lumina of the glands, occasioned by swelling and desquamation of epithelial cells. It is probable, however, that the diminished

secretion is partly dependent on a deranged state of the nervous system.

The clinical effects of a diminished secretion of succus entericus are important, and are due to the constipation which is the chief effect of this diminution. We do not know just how great is the *rôle* of this diminished secretion in causing constipation, but it is probable that the majority of persons who suffer from chronic constipation suffer also from a diminished secretory activity of the intestinal glands. It was found by one observer that the action of the succus entericus upon starches was distinctly delayed in catarrhal inflammation of the intestine, but of course this influence is of little importance in comparison with the constipation which it occasions. It is probable that diminished secretion of the succus entericus and diminished motility of the intestinal walls are conditions that commonly develop simultaneously. I shall again refer to this relationship in speaking of the constipation that attends diminished motility in the intestine.

An increase in the succus entericus was supposed by Cohnheim to occur in cholera. There is certainly a large increase in the secretion of fluid from the intestine in this condition and in many states attended by diarrhœa, but it is difficult to say whether the fluid has the character of the succus entericus or whether it is simply a very watery serous fluid possessing the features of a transudation rather than those of a secretion. In conditions attended by a free flow of fluid from the intestinal mucous membrane this secretion or transudation may be of considerable importance in removing toxic substances from the blood. Thus iodides, bromides, bichloride of mercury, carbolic acid, and perhaps morphine may be removed through this channel. In cases of chronic nephritis with uræmia the diarrhœal discharge may contain urea.

In reviewing the disorders of intestinal secretion it remains for me to speak of conditions attended by the increased formation of mucus. The intestine contains numerous mucous glands, and a small quantity of mucus is normally thrown into the intestine, where it is probably of some use in contributing bulk and in giving a smooth surface to the intestinal contents in the colon. There is no reason to suppose that diminished secretion possesses any marked pathological significance, although it may contribute, in

association with diminished succus entericus, to the production of constipation. The opposite condition, however—namely, one of increased secretion of mucus—is by no means uncommon, and may be evidence of disease of the mucous membrane. Any catarrhal inflammation in the small or the large intestine is liable to be attended with a considerable increase in the secretion of mucus, which is very evident in the stools. Most of the mucus comes usually from the colon, where the mucous glands are numerous. It is important for you to remember that considerable mucus in the fæces may come from a stomach which is the seat of chronic mucous gastritis. The mucus is then apt to be intimately mixed with fæcal material. Mucus coming from the colon is more apt to be irregularly distributed through the fæcal material. The presence of superficial ulcers in the colon may give rise to very large quantities of mucus in the fæces, the surface of the ulcers becoming thickly coated with a mucous secretion. The mucus derived from superficial ulcers is often in considerable masses, which are separated from the rest of the fæcal matter. In the condition known as mucous colitis the stools contain a large quantity of mucus at irregular intervals. In some instances of this sort there are large casts of the intestine, consisting of layers of mucus, epithelial *débris*, and leucocytes. Sometimes these casts are many inches in length. Probably there is some superficial ulceration of the mucous membrane of the colon in these cases. Mucous colitis is very frequently seen in nervous or hysterical persons, and the disturbance of the nervous system is thought to be in some way connected with the formation of this excess of mucus. Discomfort in the colon often attends the dislodgment of mucous casts, but after the passage of these masses patients are apt to be greatly relieved for a time, both from local discomfort and various nervous symptoms, such as mental depression. These cases of mucous colitis are commonly very persistent, but may entirely clear up under suitable treatment. The treatment includes the washing of the colon for the removal of the mucus, the use of simple food containing non-irritating substances, the use of tonics, and, above all, an out-of-door life free from worry.

We have now considered the leading disorders of secretion, and have to take up the disturbances which show themselves in an altered motility of the intestinal tube. An

increase in the activity of the muscles of the intestinal wall gives rise to two principal symptoms—colic and diarrhœa. Colic consists in sudden and griping—often very severe—paroxysms of pain, dependent on a temporary excessive contraction of the intestine at some one point. Probably colicky pains are sometimes produced by spasm at the pylorus. The pain of colic is sometimes so severe as to cause collapse with clammy sweat, pallor, very feeble pulse, &c. More often the paroxysms are less severe, and do not give rise to general symptoms.

The pain of colic is usually due to a contraction of the unstriped muscular fibres of the intestine in the attempt to push onward some mechanical or chemical irritant. The pain is relieved by the successful passage of the offending material. The mechanical irritants concerned in causing colic are frequently unripe fruit, coarse bread, nuts, shell-fish, or some other form of food not readily broken up by the digestive juices. The pain comes on so rapidly in some instances after the eating of these indigestible foods that there is no doubt of the dependence of the pain on mechanical irritation rather than on chemical products. The accumulation of gas in the colon is perhaps the commonest cause of colic. The chemical irritants which cause colic are varied in character, but generally consist in products of carbohydrate fermentation from improper feeding. In consequence of the decomposition in carbohydrate food irritating acids are formed, among them lactic, butyric, and acetic acids. It is to the presence of these acids that the colic can sometimes be referred. In some persons alcohol in almost any form will give rise to colicky pains. There are also individuals in whom the use of fluids of any kind, especially if they be cold, is followed by griping pain. The irritant action under these circumstances depends on the bulk and coldness of the ingested fluid. When colic is due either to mechanical or chemical irritants taken in the form of food, there is usually an increased peristalsis throughout the intestine, which results in soft or diarrhœal movements. Where chemical irritants are concerned, the acids mentioned above may be found in the evacuation. It should be clear to you from what has just been said that colic is the expression of a conservative reaction on the part of the intestine, which has the effect of removing offending materials from the body. The susceptibility to the development of colicky pains varies

much in different persons, and in the same person at different times.

You are of course aware that constipation is sometimes a cause of very severe colic, due to efforts on the part of the intestine to dislodge hard fæcal masses. Constipation is, perhaps, the chief cause in the production of colic in lead poisoning. Here the lead salts probably contribute to produce constipation by checking intestinal secretion.

The commonest and most important clinical result of increased intestinal motility is diarrhœa. Diarrhœa, or the occurrence of fluid movements, is to be regarded as the expression of a motor reaction of the intestine to irritants. The symptom has many causes. We usually think of diarrhœa as resulting either from diminished absorption of water from the intestine, to increase of secretion from the intestinal mucous membrane, or to both causes together. Many purgatives, as cascara, castor oil, and calomel, act largely by stimulating the peristaltic movements of the intestine. In consequence of these the materials in the intestine are hurried along without the usual opportunity for the absorption of water. The result is a diarrhœal movement. On the other hand many salts act also by abstracting water from the blood. The fluid coming through the mucous membrane of the intestine adds considerably to the fluid content of the gut, and together with the increased peristalsis gives rise to loose movements.

Most diarrhœas depend upon the use of food which is not well adapted for digestion. Foods act either as mechanical or as chemical irritants, sometimes as both. Often the diarrhœal discharges from improper food are referable to the formation of chemical irritants. Thus, in the course of excessive fermentation of carbohydrates fatty acids are formed which are capable of actively increasing peristalsis. The movements then contain acetic and other acids. The quantity of carbohydrate food which is necessary to induce a diarrhœa of this character varies with the condition of the patient. A normal person can take a much larger quantity of sugar or of starchy food without any indications of diarrhœa than one who has chronic catarrhal enteritis. Many persons regularly develop diarrhœa after a large carbohydrate meal. I am inclined to suspect that these persons are already suffering from catarrhal enteritis of a persistent character, and that fermentation sets up an acute exacerbation,

perhaps slight, which is responsible for the appearance of watery movements. Although the carbohydrates are the most frequent cause of diarrhœa from food, the proteids are sometimes responsible for severe diarrhœal seizures. We do not understand fully the order of events in the production of diarrhœa from excessive proteid putrefaction. Neither do we know just which products are usually concerned in such diarrhœa. It has been experimentally shown in the human subject that one important product of excessive proteid putrefaction, namely indol, is capable of setting up diarrhœa, and it seems to me possible that this substance sometimes plays a part in producing such disturbances. There are probably numerous irritant substances produced by proteid putrefaction, which are capable of acting in the same way as indol when produced in marked excess. It is conceivable that ammonia, phenol, and cresol are capable of acting in this way, although we have no definite information. Then, again, it is probable that in some instances specific poisons are produced as the result of unusual putrefactive conditions outside or inside the intestine. Thus tyrotoxicon present in poisonous cheese is capable of inducing diarrhœa. The muscarine contained in some mushrooms is also capable of exciting diarrhœa. The chemical factors in the diarrhœal discharge observed in typhoid fever and in cholera are not yet known to us. Under exceptional conditions alcohol appears capable of inducing diarrhœa. It is likely that this poison acts by first setting up a chronic gastro-enteritis, which in turn leads to impaired digestion of food-stuffs, with the formation of chemical irritants from carbohydrate fermentation. Alcohol may also act as a direct cause of diarrhœa where a chronic gastro-enteritis exists, but this is an unusual effect.

How far the products of anaërobic bacterial action may be concerned in the production of diarrhœa we do not know.

Where a diarrhœa becomes chronic there is generally reason to suspect that structural alterations in the intestine are the cause of the persistence of this symptom. We must carefully exclude the various causes of an organic nature before concluding that diarrhœa of chronic character is due mainly to improper food.

In some persons with chronic nephritis associated with a marked increase in the urea of the blood-serum the urea is excreted to an extent vicariously by the intestine. The

excretion of urea from the intestinal mucous membrane always occasions diarrhœa, usually diarrhœa of an intractable nature. Uræmic diarrhœa is accompanied by congestion of irregular distribution in the mucous membrane of the large and small intestines. This congestion, which is sometimes intense, seems to be closely connected with the process of transudation of urea from the blood into the gut. Such a congestion, with the accompanying diarrhœa, can be very easily brought about in an experimental way by making infusions of urea into the circulation in dogs.

Very often it happens that the movements in the diarrhœa of children are distinctly green in colour. This abnormal colour is thought to be dependent on an abnormal alkalescence of the intestinal contents which favours the change from bilirubin, the brown colouring-matter of the bile, to biliverdin, the green colouring-matter. The green colour of the stools is especially apt to occur in children that are being fed on milk, and the stools often contain lumps of undigested casein. Under these circumstances the milk ration should be decreased or stopped. The view has also been held that the green coloration of the stools depends upon a special micro-organism which produces a green pigment, but there does not appear to be satisfactory evidence in support of this explanation.

The term 'fat diarrhœa' has been applied to stools containing a very great excess in fat—40 or 50 per cent. of the dried substance, instead of 15 to 20 per cent., as in health. Such stools are light in colour and usually voluminous. They are commonly soft in consistence, but do not give rise to diarrhœa in the ordinary sense of the word. Such fat stools are observed mainly under conditions that give rise to a diminished access of bile to the intestine. Microscopical examination shows that the fæces contain very large numbers of fatty acid crystals or crystals of sodium and calcium and magnesium soaps.

The chief effect of diminished motility in the intestinal tract is constipation. This condition of delayed evacuation of the contents of the intestine exerts an important influence upon the general health when it is persistent. We do not know at present all the effects of prolonged constipation, nor do we know how the deleterious influences are produced. We know, however, that in many persons constipation gives rise to headache and various unpleasant cephalic sensations,

and that it occasions mental depression and a variety of neurasthenic symptoms. The effects of constipation certainly vary widely with individual susceptibility. It has been thought that one of the common results of constipation is anæmia, and that the chlorosis of young women is very largely referable to it. It is by no means clear, however, that in cases of chlorosis the constipation is not one of the results of the anæmia. We can only say that the association of constipation and chlorosis is very common, and that the relief of the constipation is a condition essential to recovery. We have not as yet evidence to justify us in assuming that constipation is in itself an adequate cause of chlorosis.

We have still a good deal to learn about the way in which constipation of a prolonged character gives rise to symptoms of disease. I mentioned on a previous occasion that chronic constipation is usually attended by an increase in the putrefactive products that result from the breaking down of proteids. This increase in intestinal putrefaction is associated with the formation of an excessive quantity of aromatic and other substances. The absorption of these substances is followed by their presence (or that of their derivatives) in the blood, and by their excretion in the urine. During the time when these aromatic products circulate in the blood they have an opportunity to modify the normal activities of the cells generally, including those of the nervous system. It is probably in consequence of this that the various nervous symptoms of constipation arise. Just what products are chiefly concerned in producing the headache, mental depression, nervousness, &c., incidental to constipation, we cannot at present state with positiveness.

There is one effect of constipation which is of considerable pathological interest, though it has received little attention. This is an increase in the amount of urobilin in the urine. Owing to the slow absorption of the fæcal urobilin, the maximum effect of constipation on the urinary urobilin is not usually observed for two or three days. Moreover, in conditions attended by diminished secretion of bile, we fail to find the urobilin of the urine increased. There are many anæmic and constipated persons in whom the urine contains less than the ordinary amount of urobilin, and I am inclined to ascribe this to a diminished secretion of bile-pigments, referable to the low hæmoglobin content of the blood. It must be owned that writers are not yet in accord as to the

effect of constipation on the urobilin of the urine, and that further studies are much to be desired.

I have told you that diminished peristalsis is the commonest cause of constipation. Let us consider some of the causes of this reduction in peristaltic activity.

A common cause of constipation is the use of food containing too much proteid and too little fat and carbohydrate material. This is common in children. So little material is left unabsorbed that what remains is insufficient to stimulate the wall of the intestine to normal activity. The innervation of the intestine may be quite normal, but peristalsis is reduced because of the absence of sufficient stimuli. The free use of milk is often responsible for constipation of this kind. We also see in adults on a restricted diet that constipation is very easily induced by the use of a disproportionately large amount of proteid food with insufficient carbohydrates and fats.

You know that water is a powerful peristaltic stimulant, especially when it is drunk at a low temperature. Some persons avoid water and fluids in general because their use is followed by uncomfortable sensations in the abdomen. If the restriction be considerable, constipation regularly follows the withdrawal of this normal physiological stimulus. The same effect may be brought about in quite a different way. Excessive evaporation from the skin, under the influence of prolonged exposure to the air, may lead to a marked reduction in the normal amount of fluid in the stomach and intestine, in consequence of which constipation is very readily induced. We see this in persons who ride long distances on horseback or who take long walks. Profuse perspiration of course favours the development of constipation.

A highly important cause of constipation is the muscular relaxation of the walls of the intestine. We are by no means fully informed of the manner in which this effect is produced. It appears to be dependent on defective innervation, and this in turn seems liable to arise from any conditions that are capable of debilitating the nervous system. Excessive fatigue, mental or physical, may have this influence. The condition is often seen in neurasthenic patients. Sexual excitement in some persons distinctly promotes this disturbance of innervation. The muscular relaxation may be purely functional in character, unattended by definite alterations in the position of the bowel. Such cases recover readily when the causes of impaired innervation are removed. In

many instances, however, the impaired innervation is associated with an alteration in the position of the colon or small intestine. Here the element of mechanical obstruction is added to the atony of the intestinal wall. Cases of this kind are naturally much less amenable to treatment than those which I have just referred to, and represent a cause of constipation which often baffles one's therapeutic skill.

I have already mentioned to you the influence of a diminished secretion of bile and of the succus entericus in occasioning constipation. These disturbances in secretion are very apt to be associated with atony of the muscular walls of the intestine. It is not unlikely that the withdrawal of the habitual stimulus of these secretions is one cause of intestinal atony.

I have found that an improvement in digestion, especially in the digestion of carbohydrate foods, is frequently followed by constipation. It may appear to you paradoxical that constipation should ever be the consequence of an improved state of the digestive tract, but this is undoubtedly the case. There are many persons who suffer from excessive fermentation of carbohydrates. This excessive fermentation leads to the formation of large soft masses of fæcal material in which there is often considerable gas which has been set free in the course of the fermentative process. These soft movements, which frequently have a strongly acid reaction from the presence of free fatty acid, secure to the patient a regularity in movements, perhaps in spite of the fact that there is some degree of atony of the intestinal wall. If now the digestion of carbohydrate food is much improved through out-of-door life, exercise, &c., the excessive fermentation may cease, and in consequence of the diminished formation of fatty acid, gas, &c., the contents of the large intestine become firm and hard and difficult to expel. Of course this constipation may be aided by excessive evaporation from the skin, but in many instances I believe that it arises mainly because fermentation of the intestinal contents is reduced.

An important though not very frequent cause of constipation is inanition. Whenever the intake of food is greatly reduced the formation of fæces becomes very much diminished, and on a small quantity of food the bowels are obstinately constipated. Of course it is usually obvious enough that the constipation is really due to starvation, but it sometimes happens that the real cause is overlooked. Thus in nursing

children it is not always easy to feel sure that enough milk is being taken unless the child be carefully weighed before and after the feeding. I have known the attending physician to be much puzzled by obstinate constipation and loss of weight in a child that was being greatly underfed owing to the inability to draw milk from the breast. In the constipation of starvation the other indications of starvation are always present, and of these the great diminution in the chlorides of the urine is the most important.

I have now sketched for you the chief causes of constipation not due to mechanical causes. Mechanical obstacles to a free movement of the bowel are by no means rare, and it is always important in cases of chronic constipation to exclude the existence of such a cause. Fæcal obstruction in some parts of the colon is probably the commonest cause of chronic constipation of a mechanical sort. The fæcal mass can often be felt in the course of the ascending or descending colon, and it is possible to mistake it for a new growth. Such fæcal obstruction is not very infrequently associated with displacement of the abdominal viscera, especially of the colon. In a relatively small number of cases the obstruction is due to new growths, fibrous bands, or hernial malposition of the intestine. You should also know that a stenosis of the pylorus gives rise to constipation by preventing food from entering the small intestine. Where the stenosis is sufficiently marked to be the cause of marked constipation the signs of starvation in some degree are always present.

I should like to discuss with you the therapeutic indications in cases of diarrhœa and constipation, but the time at our disposal hardly permits such a discussion. I may, however, remind you of some of the leading indications for treatment. In diarrhœa from food the first thing to be done is to secure a thorough evacuation of the bowel, preferably by the use of salts or castor-oil. Then the digestive tract must be given rest, milk, or kumyss, or broths being given in small amounts at short intervals. Do not permit your patient to return too soon to the use of solid foods, and especially to fruits and vegetables. In severe cases of diarrhœa from improper food the use of 20 minims of paregoric and 5 grams of bismuth subgallate before each feeding with milk or broth may be very helpful in preventing excessive peristalsis.

I must not omit a word on the dietetic treatment of

constipation, although I am conscious of a certain element of the humorous in making the attempt to sketch the treatment of a condition so notoriously obstinate as chronic constipation. Volumes have been written on this subject, and yet when a patient presents himself with a long-standing history of constipation and a cathartic-drug habit we know very well that a quick restitution of normal physiological conditions is more than we can reasonably expect.

In most cases of simple chronic constipation the chief pathological element appears to be a diminished motility of the colon and small intestine, probably associated with diminished secretion of the succus entericus. If under these conditions it is necessary for a patient to exercise care in the quantity and quality of his food, constipation is almost certain to be persistent. As a matter of fact very many patients with chronic constipation have chronic gastritis, with diminished secretion of free hydrochloric acid. The gastritis leads to the use of bland and finely divided foods, the use of much milk, and the avoidance of coarse and bulky articles of food, such as coarse cereals, Graham bread, seed-containing fruits, &c. But the foods which are avoided on account of the gastritis and the secretory disturbance that accompanies it are just the foods a constipated patient should eat in order to provide intestinal contents of a bulky and moderately irritating character. Bulky contents of a slightly irritant character are desirable, because such contents promote peristalsis both in the colon and in the small intestine. The small hard remnants of meals adapted to gastritis fail to do this.

An important condition in the successful treatment of chronic constipation is therefore the use of food like coarse bread, coarse hominy, corn, oatmeal, vegetables rich in cellulose, and berries containing numerous seeds. Fruits of all kinds are useful on account of the slight irritant action of their organic acids. For the same reason it is wise to push to the utmost the use of carbohydrates, even if they cause somewhat excessive fermentation. The products of excessive fermentation, acetic and lactic acids, &c., are useful as stimulants to peristalsis. Butter should be consumed in sufficient amounts to make the stools contain a large percentage of fat, say from 20 to 40 per cent. of the dried substance. In young children who are being fed on milk an increase in the butter-fat is often followed by prompt improvement in the movements.

Where a diet of this kind can be instituted without delay considerable improvement may quickly follow; but where there is chronic gastritis such a diet cannot be tolerated, and nausea, local discomfort, and diarrhœa may result from attempts to live on coarse and bulky food. In such cases the task before us is to improve the state of gastritis by suitable hygienic means in order that the diet suitable for constipation can be tolerated. You will remember that, in speaking of the disorders of gastric secretion, I laid emphasis on the importance of an out-of-door life. The out-of-door life, which aids in the restoration of a gastric juice containing a normal amount of free hydrochloric acid, probably aids in the re-establishment of a normal flow of succus entericus. I told you how largely the acid-secreting function of the stomach is under the influence of the nervous system; there is every reason to believe that the secretion of the succus entericus is also in large degree influenced by the nervous mechanism. Probably the nervous conditions which permit a free secretion of the intestinal juice also favour the re-establishment of normal conditions of contractility in the intestinal walls. Certain kinds of exercise, such as walking, cycling, and horseback riding, are especially helpful in re-establishing normal intestinal motility. When the general condition of the patient improves to the point where he can eat largely of a diet containing the kinds of food already mentioned, regular movements are apt to be re-established.

The establishment of the habit of emptying the bowels at a certain time daily is of the first importance. We see the good effects of discipline in this direction both in young children and in grown persons, and we frequently see the evil effects of a lack of such discipline. It is necessary to insist that patients make regular and repeated attempts to defæcate in cases where constipation is chronic, and you must do this even where the practice entails some loss of time and inconvenience to the patient. Unless you are successful in establishing this habit in your patients, you will be compelled to resort to drugs.

Rectal Alimentation.

There is one therapeutic measure of considerable practical importance to which I have as yet made no reference in speaking of the derangements of gastric and intestinal function. This procedure is known as rectal alimentation,

and is designed to supply the organism with nutriment in cases where, for some reason, it is impracticable to give food by the mouth.

The ability to give a patient nutriment by way of the rectum depends on the capacity of the rectal mucous membrane to absorb food materials, a function which was carefully studied by Voit and Baur thirty years ago. These observers found that many preparations of animal food were at least partially absorbed when introduced into the rectum, and the results which they noted have since been repeatedly confirmed. We now know that the adult human rectum can under favourable conditions be induced to absorb carbohydrates to the extent of 50 to 100 grams in twenty-four hours, 50 grams or more of proteids, and about 10 grams of fat. Ordinarily, however, we cannot conservatively rely upon securing a greater absorption daily than would be represented by, say, 25 grams of proteid, 5 grams of fat, and 40 grams of carbohydrates. A rectal enema containing this amount of nutritive material would yield the body less than 400 calories of energy. You will recall that the average caloric needs of the resting adult are not far from 2,000 calories daily. Thus it is evident that we can supply by rectum only a small part of the nutritive material necessary for the maintenance of life. The condition of a patient relying on rectal absorption is, in fact, a condition of slow starvation, since the greater part of the nutritive potential necessary to maintain life is supplied by his own tissues. Nevertheless life is sometimes prolonged by several weeks or months by means of nutritive enemata. You may think this a questionable advantage in the case of sufferers from incurable maladies. Where, however, we have to deal with curable diseases, such as severe acute gastritis or ulcer of the stomach, or acute nephritis with irritable stomach, rectal alimentation gives us the means of at least doing something to prevent extreme prostration from inanition whilst the stomach secures the greatly needed rest.

Rectal alimentation is distinctly facilitated by the moderate digestive activities of the fluid contents of the normal rectum. The fluids of the rectum have the power of slowly converting boiled starch into dextrose, and of changing proteids into albumoses. The amylolytic or starch-splitting action is doubtless due to the presence of a ferment in the secretion formed by the epithelial lining of the lowest part

of the bowel. This secretion appears to have no proteolytic activity. But, as I just reminded you, the fluids of the rectum possess some peptonising power, and this is referable in part to the action of the colon bacilli and perhaps in part to the presence of the pancreatic ferment trypsin. Experiments have been made which render it likely that small quantities of the pancreatic ferment reach the rectum from the upper part of the intestine.

Since it is unlikely that neutral fat is absorbed as such, and since the rectal fluids do not exert a fat-splitting action, it seems probable that such limited absorption of fat as occurs from the rectum is due to the fat-splitting activity of bacteria.

Although we thus have evidence of digestive activities on the part of the fluids present in the rectum, the process of rectal digestion is always a slow one. On this account it is well to use food-materials that either require no digestion preparatory to absorption or that require only slight digestive action. Carbohydrate food can be given in small amount as glucose, which is very readily absorbed, but which in larger amounts is too irritating. The proteids are best given as raw egg albumin and as albumoses from meat or milk. One might suppose that meat albumoses such as somatose could be used abundantly; but the irritating character of the preparation, as of all concentrated albumoses, makes it necessary to use some caution about the quantity and concentration employed. Upon the whole I consider peptonised milk the best basis for rectal enemas. Neutral fat is sometimes used, but a fine emulsion of cod-liver oil is preferable on account of the greater readiness with which fat absorption occurs. On theoretical grounds one would expect good results from soft soaps, but I do not know that they have been given a fair clinical test. A much-employed nutritive enema consists of 3 eggs, 30 grams of grape sugar in 120 grams of water, 50 c.c. of claret, and 10 grams of a mixture of equal parts of flour and aleuronate. This mixture makes about one third of a litre, which is ordinarily the maximum volume that should be introduced at one time. The caloric value of such an enema is about 400 calories; but it is to be remembered that the degree of absorption to be expected varies much in different individuals. A good peptone and milk enema consists of 20 grams of peptone (meat albumoses) and

250 c.c. of milk. A useful egg and milk enema can be made with 3 eggs, 3 grams of common salt, and 250 c.c. of milk. In each case it is best to peptonise the milk. Where native proteids form a part of an enema a small quantity of sodium chloride must be added to facilitate absorption—say 1 gram of salt to each egg.

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LECTURE X

THE CHEMICAL PATHOLOGY OF HEPATIC DISEASE.—JAUNDICE

Importance of the hepatic functions—Disturbances of the bile-forming functions as expressed by jaundice—Historical landmarks in the development of the hæmatogenous theory of jaundice—Observations of Reil, Saunders, Frerichs, Kühne, and Virchow—Reasons for the untenability of a purely hæmatogenous hypothesis of jaundice—Evidence that the liver is the chief seat of formation of bile colouring-matter—Experiments of Naunyn and Minkowski – Obstruction of bile-ducts in supposedly hæmatogenous jaundice—Experiments with toluylendiamin—Viscidity of the bile in certain cases of human jaundice where there is excessive destruction of blood—Relation between destruction of red blood-cells and jaundice—The two principal types of jaundice—Possibility of the existence of other forms—Causes of jaundice from obstruction of the larger bile-ducts—Causes of hæmohepatogenous jaundice—Clinical characters of the two types—Phenomena dependent on the presence of the bile elements in the blood—Pigmentation of skin and other tissues—Excretion of bile-constituents in the urine—Bilirubinuria—Origin of urobilin—Variations in pigmentation of skin, urine, and fæces in different grades of obstruction—Cholæmia—Influence of the bile-acids in the production of toxic symptoms—Explanation of the diminution or absence of the bile-salts in the urine of jaundice—Influence of the bile colouring-matters and of cholesterin—Effect of the toxæmia of jaundice upon general metabolism – Effects of exclusion of the bile from intestine—Recapitulation, or the differences between obstructive and toxæmic jaundice—Importance of correct diagnosis of the cause of jaundice—Medical treatment of jaundice.

I INVITE you this morning to review with me some of the more important disturbances connected with the pathological chemistry of diseases of the liver. This is a subject of very great practical and theoretical interest, but I cannot hope to do more than to sketch for you the more essential processes involved in disorders of hepatic activity.

Probably no organ in the body performs such a variety of essential chemical functions as the liver. It is the seat

of formation of the constituents of the bile, the storehouse for glycogen, the place where oxidative processes go on with the greatest activity and with the liberation of the greatest amount of heat, the seat of numerous synthetic processes of fundamental importance like the formation of urea, and in a general way the place in which the processes of detoxication go on with the greatest energy. The liver may, without exaggeration, be likened to a sentry constantly on guard to screen the nervous system and other parts of the body from the toxic effects of substances manufactured in the intestinal tract. The liver is, moreover, a highly important excretory organ, which not only exerts the important physiological action of disposing of at least a part of the hæmoglobin of disintegrating red blood-cells by converting it into the bile colouring-matters, but is further capable of rendering important assistance as an excretory organ in ridding the body of bacteria. Some of the functions of the liver are highly special in character, others it shares with the parenchymatous organs generally, and with the muscles.

To-day I wish to speak of those disturbances of hepatic function that are connected with the secretion of the specific product of the liver-cells—namely, the bile. The patbological chemistry of the bile-forming functions of the liver can best be outlined in a study of jaundice.

Jaundice is, as you know, a common disturbance, indicative of disorder either of the hepatic functions alone or of disease of the liver and the blood together. It is characterised clinically by a yellowish pigmentation of the skin with the bile colouring-matters and by the presence of bile-pigments in the urine with or without the bile-acids. The pigmentation of the tissues of the body depends on absorption of bile from the bile-ducts into the lymphatics and blood, and this absorption is a result of obstruction to the normal flow of bile from the bile-passages.

The yellow coloration of the skin in jaundice is such a striking feature that it has long occupied the attention of clinicians and pathologists. I think I cannot do better than to outline for you some of the more important phases in the history of our knowledge of jaundice. It seems to me very instructive and interesting to consider the chief steps by which we have come to our present conception in regard to the pathology of this somewhat complex condition.

The connection between obstruction to the exit of the bile and jaundice has long been recognised, it being sufficiently obvious that the accumulation of bile under pressure should give rise to the passage of bile into the blood and thence into the skin. On the other hand, it has long been known that instances of jaundice are by no means rare in which the common bile-duct and the larger bile-ducts are entirely free, and in which no evidence of obstruction can be detected. Cases of this sort have been the subject of much speculation. So long ago as 1782 Reil gave a description of the jaundice which is unconnected with obstruction. He noticed that the movements in such cases might contain a large quantity of bile colouring-matter in spite of the fact that there is jaundice. From this he inferred that there could be no obstruction to the outlet of the bile. Further observations on cases of this sort were made by Saunders in 1809, which resulted in a confirmation of Reil's view that jaundice might be unconnected with obstruction. Saunders even suggested that the jaundice might arise from disease of the blood, thus vaguely foreshadowing the more modern theory of hæmatogenous jaundice.

In 1858 the German clinician Frerichs first developed the idea that jaundice is dependent on an altered state of the blood. His view was that the bile-acids, sodium glycocolate, and sodium taurocolate, are normally changed in the blood into the bile-pigment, and that any condition which impairs the oxidative activities of the blood interferes with the formation of the normal bile-pigments and leads to the production of abnormal colouring-matters which are deposited in the skin and give rise to jaundice. Frerichs supported this theory of the nature of certain cases of jaundice by the important observation that if bile-salts be injected into the circulation of dogs these salts disappear, while bile-pigments are found in the urine. He concluded, somewhat hastily, but perhaps not unnaturally, that the bile-salts were converted directly into bile-pigment.

The observation that bile-salts injected into the blood in dogs leads to the presence of bile-pigment was quickly confirmed by Kühne. But Kühne placed an entirely different interpretation upon the fact. He found that the infusion of hæmoglobin into the blood was followed by the appearance of bile-pigment in the urine, and very soon

satisfied himself that the bile-salts act in the manner described by Frerichs owing to the fact that they liberate hæmoglobin by the destruction of red blood-cells. He further made the important generalisation that all agents which operate by liberating an excess of hæmoglobin in the blood are capable of causing the presence of the bile-pigments in the urine, and may even be followed by jaundice.

Virchow had made a discovery in 1847 which apparently gave the strongest kind of support to the idea that jaundice may arise from changes in the blood independently of disorder of the liver. This discovery consisted in finding crystals of hæmatoidin in old extravasations of blood. You know that hæmatoidin is derived from hæmoglobin, and resembles bilirubin in this respect as well as in chemical composition. The very close resemblance between these two substances made it natural to suppose that a transformation of hæmoglobin into bilirubin, like the change from hæmoglobin to hæmatoidin, may occur through alterations in the blood quite unconnected with any intervention of the liver. It was therefore assumed that jaundice may arise from such a conversion of hæmoglobin into bilirubin without the intervention of the liver. This was the theory of hæmatogenous jaundice—that is, the view that jaundice may have its origin in destruction of the blood—a doctrine which came to be rather widely accepted by pathologists and clinicians, and still has a considerable hold on the minds of practitioners. The hæmatogenous doctrine received support from the statement of Leyden, that in cases of obstructive jaundice the bile-salts appear in the urine, whereas they are not found in the urine of patients with jaundice of the non-obstructive variety. The inferences which were made from Leyden's observation on the bile-salts were as follows:—The bile-salts are formed in the liver; therefore when no bile-salts are formed the liver must be inactive, and if the liver is so inactive that it does not produce bile-salts it must be true that the bile-pigments in cases of jaundice are derived, not from the liver, but from the blood.

This doctrine of the hæmatogenous origin of jaundice thus seemed to be firmly grounded, but facts very soon came to light which made the doctrine no longer tenable. Virchow, one of the chief founders of the hæmatogenous doctrine, was one of the first to abandon it.

There are two facts which experimental study has established which make the existence of a purely hæmatogenous jaundice most improbable. These are, first, the fact that the liver is the chief seat of formation of the bile colouring-matters; and secondly, that the jaundice produced by blood poisons which destroy red blood-cells, with the liberation of hæmoglobin, may alter the bile in consistence, so as to produce an obstruction in the small bile-ducts which is due to the increased viscidity of the bile.

That the liver is the seat of the formation of bile-pigment was shown by the experiments of Minkowski and Naunyn. These observers found that when geese were poisoned with arsenuretted hydrogen (AsH_3) large amounts of bile-pigment appeared in the urine, owing to the liberation of hæmoglobin. They did not find free hæmoglobin in the urine, unless the destruction of red blood-cells was very great. Having established these facts they repeated the experiment with one important modification—namely, with extirpation or ligation of the vessels passing to the liver. Under these circumstances—that is to say, where the functions of the liver are eliminated and the animal is poisoned with arsenuretted hydrogen—the bile colouring-matters no longer appeared in the urine. Instead, there appeared in the urine large quantities of hæmoglobin. The conclusion from these experiments is clear. It is that the liver normally transforms hæmoglobin into the bile colouring-matters, biliverdin and bilirubin. If the bile colouring-matters were really formed in the blood from hæmoglobin, they should continue to be formed when the functions of the liver have been eliminated.

Let us now consider the second fact which renders a purely hæmatogenous jaundice most improbable—namely, that the jaundice resulting from blood poisoning is associated with obstruction in the smaller bile-ducts. This fact was first established by Stadelmann by making use of the substance known as toluylendiamin. When this substance is injected into a dog it occasions a great destruction of red blood-cells, bile-pigments appear in the urine, the quantity of bile-pigment in the bile is very much increased, and the animal becomes intensely jaundiced. The increase in the pigments of the bile is found from two to twelve hours after the injection. Between the fourteenth and sixtieth hour the quantity of bile grows much less, loses the character of bile,

and resembles extremely viscid colourless mucus. This viscid condition of the bile apparently arises from a catarrh of the intra-hepatic bile-ducts, due either to the toluylendiamin or some derivative of this poison. It is important for you to understand that a duodenal catarrh does not necessarily exist in these cases of experimental jaundice, and that the larger bile-ducts may be comparatively little implicated in the catarrhal process.

We may picture to ourselves the sequence of events as follows: First, the destruction of hæmoglobin and the increased formation of bile-pigments; secondly, an increase in the viscidity of the bile with temporary obstruction in the smaller ducts and an accumulation of pigments in the blood, giving rise to jaundice; and thirdly, a diminution in the action of the poison on the bile-ducts, from which the bile grows less viscid, the obstruction stops, and the bile-flow is re-established, while the jaundice quickly disappears.

Here, then, we have a jaundice which might be regarded as purely hæmatogenous, but which really depends ultimately upon obstruction in the smaller ducts of the liver. If this result related only to dogs poisoned by toluylendiamin, these observations would not possess much practical interest. But the truth is that this experimental jaundice serves as a type of many cases of human jaundice where there is excessive destruction of blood, as, for instance, in pyæmia, malaria, acute yellow atrophy of the liver, &c. In many of these cases a viscidity of the bile has been discovered which certainly suggests very strongly that in the jaundice with excessive destruction of blood the pigmentation of the skin is a consequence of obstruction in the bile-ducts. These cases are therefore hepatogenous; that is, due to liver disease; but in order to indicate the presence of the important element of excessive destruction of blood, we may speak of these cases as hæmo-hepatogenous. Or, if we choose to be wholly non-committal as to the part which the liver plays in causing this kind of jaundice, we may speak of it as toxæmic. I advise you to discard the term 'hæmatogenous jaundice' altogether.

Although it seems to me that the balance of evidence favours the view that these cases of toxæmic jaundice are dependent on obstruction due to the viscid contents of the bile-ducts, it is only proper that I should tell you that this view has not been universally accepted. Thus one observer

has reached the conclusion that in dogs that have been poisoned with toluylendiamin the increase in the consistence of the bile occurs too late to account for the development of the jaundice. I am inclined to think that this objection to the conclusions of Stadelmann, Hunter, and others cannot be sustained. Nevertheless it is held by some writers that the true explanation of the jaundice lies in a peculiar secretory anomaly of the liver cells, by which the bile-pigments, instead of finding their way into the usual channels, the bile-ducts, escape into the lymphatics, and thus find their way into the blood. I do not think there is much to be said in support of this hypothesis, but I mention it to you in order to show you that the obstructive theory of toxæmic jaundice is not without its opponents. Moreover it is possible that this explanation holds true of a small class of cases of jaundice—as where jaundice persists for a long time after the removal of the cause of obstruction in cases due simply to obstruction of the common bile-duct.

You will very naturally ask, What is the relation between the destruction of the red blood-cells and the development of jaundice? If it be true that in toxæmic jaundice there is a great destruction of red blood-cells, one might perhaps presume that there is a direct relationship between the extent of the blood destruction and the jaundice. As a matter of fact, the relationship between blood destruction and jaundice is by no means a close one, and I will try to explain to you why this is the case.

When there is a very large destruction of red blood-cells this is followed by hæmoglobinuria, or the appearance of hæmoglobin in the urine. It has been estimated that hæmoglobinuria results only where the destruction of about one-sixtieth of the entire blood has rapidly taken place. The reason why hæmoglobinuria follows great blood destruction is simply that the liver is unable to transform the hæmoglobin into bile-pigment rapidly enough to prevent the passage of hæmoglobin out of the blood by way of the urine. The liver can transform an amount of hæmoglobin much larger than it is called upon to transform under normal conditions, but after a certain point is reached this function of the liver is no longer adequate to the greatly increased task, and the unchanged hæmoglobin enters the urine. Even where the destruction of blood is so excessive as to cause hæmoglobinuria there may be no jaundice whatever. We

see this in paroxysmal hæmoglobinuria and after the injection of water into the veins, a procedure which gives rise to very great blood destruction. On the other hand, we sometimes see extreme jaundice without any hæmoglobinuria, as in icterus gravis, Weil's disease, or toluylendiamin poisoning in dogs. Here there is less blood destruction than in the cases to which I first referred. Nevertheless there is jaundice.

It seems clear from what I have just said that some special factor must enter into the occurrence of toxæmic jaundice, quite distinct from the extent of the blood destruction. It is probable, as I have already intimated, that this factor consists in the ability of the blood-destroying poisons to set up a catarrhal inflammation of the small bile-ducts, and through this to give rise to obstruction to the exit of the bile.

There are thus two principal classes of jaundice. First, the class of cases in which the jaundice depends on a gross obstruction of the largest bile-duct, without a greater destruction of blood than is normal, and secondly, cases in which the obstruction depends on an increase in the viscidity of the bile in the smaller ducts, and in which there is a pathological destruction of red blood-cells.

Whether jaundice ever arises in any other way than through the processes I have sketched I am unable to tell you positively. One is certainly justified in suspecting that other forms of jaundice occasionally arise. Thus an extensive abscess of the liver is often associated with slight jaundice unconnected with obstruction of the larger ducts, and also independent of any considerable blood destruction. It is possible that in these instances of extensive destruction of liver-cells the normal secretory processes may be so deranged that the bile finds its way into the blood in sufficient amount to give rise to slight jaundice. Then, again, there is another possible origin of certain cases of jaundice. You know that it is very common for a slight degree of jaundice to occur in the first days of life. Different explanations have been offered as to the nature of the jaundice, and many writers consider the condition toxæmic in origin and associated with an excessive destruction of red blood-cells. One cannot but suspect that the initial infection of the gut with bacteria in the first days of life may in some way be connected with the occurrence of icterus

neonatorum, but there are as yet no substantial grounds on which to base this idea.

The explanation has also been suggested that the jaundice of the newly born is due to the fact that the bile absorbed from the intestine finds its way in part into the general circulation owing to the failure of the *ductus venosus* to close. You remember that the *ductus venosus* permits some of the fœtal blood to pass from the portal vein into the inferior vena cava, and that this communication normally closes in the first few days of life. If this channel of communication between the portal vein and the vena cava should remain open longer than usual, it would explain the passage of bile colouring-matter into the blood, and its deposit in the skin. As a matter of fact the *ductus venosus* was found patent in a case of icterus neonatorum which came to autopsy. I have mentioned the possibility of jaundice arising in consequence of this mechanical peculiarity in the circulation, simply to illustrate the possibility of jaundice arising in other ways than those I have already mentioned to you, and not because it possesses any considerable practical interest.

Probably more than four-fifths of all the cases of jaundice that one meets in the course of a practice in the temperate zone are dependent on obvious mechanical obstruction, that is to say, are purely hepatogenous. These cases include the jaundice due to gall-stones, hydatids, foreign bodies in the duct, inflammatory tumefaction of the duodenum, stricture of the common bile-duct, tumours compressing the orifice of this duct, compression of the duct through new growths in the stomach, pancreas, or kidney, pressure by aneurism, or fæcal masses in the colon, pressure by the pregnant uterus, uterine tumours, &c. In these cases if the obstruction be complete, the jaundice is very intense. Unless there be fever dependent on complications, there is little or no elevation in temperature.

The cases of toxæmic or hæmohepatogenous jaundice are met with under conditions different from those which give rise to obstructive jaundice. They occur in the course of diseases attended by excessive destruction of red blood-cells, as, for example, in yellow fever, severe malaria, typhoid fever, typhus fever, and scarlet fever. They also arise in the course of other presumably infectious diseases, as in the condition known as epidemic jaundice, in Weil's disease, and in

acute yellow atrophy of the liver. This class of cases also differs from that of simple obstructive jaundice in the clinical manifestations. Fever and delirium are common, owing doubtless to the presence in the blood of bacterial poisons. Moreover the signs of a toxæmia associated with excessive destruction of blood may be present. These signs include hæmorrhages from the nose, stomach, or gut, and hæmoglobinuria. The jaundice itself is apt to be much slighter than in cases of marked mechanical obstruction. This slighter jaundice appears to be referable to the fact that the obstruction in the bile-ducts is not complete. In fact the fæces often contain a large amount of bile colouring-matter, and this in itself is an indication that the larger bile-ducts are patent. There may even be a marked excess in the quantity of bile-pigment, due to the greatly increased formation of bile-pigment from the blood destruction. This excess of bile-pigments in the fæces is described as polycholia. The term 'polychromia' is a preferable one to 'polycholia,' because the increase in the bile is due to the increase in pigment matter, and is not known to include any increase in the bile-salts and other constituents of the bile.

We are now in a position to consider in some detail the clinical phenomena connected with the impaired excretion of bile that occurs in jaundice. These phenomena can be conveniently divided into two groups: first, those which depend on the presence of the bile-elements in the blood, and second, the group of disturbances caused by the exclusion of the bile-secretion from the intestine. There are three sets of symptoms or conditions that arise from the presence of the bile-elements in the blood: first, those due to the deposit of bile colouring-matters in the skin and other tissues; second, those connected with the excretion of the bile-constituents in the urine; and third, the functional disorders in various organs that depend on the poisonous action of constituents of the bile, *i.e.* phenomena of cholæmia in the narrow sense of the word.

The deposit of the bile colouring-matters, and especially of bilirubin, in the skin is the cause of the yellow tint of jaundice. A slighter pigmentation takes place in some of the other tissues. These tissues, however, do not readily take up the bile-pigment. Much of the coloration observed in the internal organs after death is apparently due to post-mortem imbibition. It has been shown experimentally that

the muscle-cells, the fat-cells, and the cells belonging to the walls of the blood-vessels take up the bile colouring-matters only after death has occurred. In obstructive jaundice the pigmentation of the skin and tissues not only develops slowly, but develops rather more slowly than one might anticipate. Thus Frerichs found that from twenty-eight to forty-eight hours elapsed before the pigment could be found in the blood plasma after tying the common bile-duct in dogs. In the case of the human subject it is estimated that two or three days pass before the conjunctivæ are tinged yellow or the pigment appears in the urine. In some cases of jaundice, however, especially those connected with biliary colic, less than twenty-four hours have elapsed between the onset of the obstruction and the pigmentation of the skin. It is suggested that in these cases the pigmentation is hastened by the pressure exerted in consequence of a strongly contracted gall-bladder, the pressure being favourable to the absorption of the bile.

The excretion of certain bile-constituents in the urine occurs in all varieties of jaundice. It is essential to distinguish carefully between the appearance of colouring-matters in the urine and the appearance of the salts of the bile-acids.

The bile colouring-matters find their way into the urine because these colouring-matters are present in the blood, and they owe their presence in the blood to the fact that the liver continues to produce bile colouring-matters even in the presence of complete obstruction of the common bile-duct. Indeed the liver not merely produces these bile-pigments, but often produces them in considerably increased quantity in cases of toxæmic jaundice with marked destruction of red blood-cells.

The principal colouring-matter that finds its way into the urine is bilirubin ($C_{16}H_{18}N_2O_3$), and is derived, as I have already mentioned, from hæmoglobin through the intermediate stage of hæmatin. From the following equation you can see the relationship between hæmatin and bilirubin:—

$$\underset{\text{Hæmatin}}{C_{32}H_{32}N_4O_4Fe} + 2H_2O - Fe = \underset{\text{Bilirubin}}{C_{32}H_{36}N_4O_6 \text{ or } C_{16}H_{18}N_2O_3}$$

The quantity of bilirubin in the urine is often considerable and gives it the distinctive yellowish-brown coloration with which you are familiar. The presence of bilirubin is

shown by the addition of oxidising agents like nitroso-nitric acid, which convert the bilirubin to biliverdin, which one recognises by its green colour.

Perhaps you will be surprised when I tell you that the urine of patients with jaundice does not always contain bilirubin. During the stage of convalescence from ordinary obstructive jaundice a time comes when the bile-pigments are again discharged through their normal outlet into the intestine. The bile-pigments at this time disappear from the urine and reappear in the fæces. The yellow coloration of the skin now begins to fade, but several days or even weeks may elapse before the pigmentation of the skin ceases. On the other hand we sometimes find the bile-pigment in the urine in considerable amount, and for many weeks without the occurrence of the pigmentation in the skin. This happens, for instance, in some cases of cirrhosis of the liver.

But bilirubin is not the only colouring matter that finds its way into the urine in jaundice. In many instances urobilin is also present. The urobilin found in the urine of certain patients with jaundice has been regarded by some writers as a variety of urobilin distinct in composition from that urobilin which we find in the urine of persons in health —pathological urobilin it has been called. Now, when we come to examine the evidence on which the doctrine of pathological urobilinuria is based, we find that it is far from convincing. Normal and pathological urobilin have been described by McMunn, by Eichholz, and by Jolles; but the methods employed by these observers for the separation and purification of pathological urobilin make it probable that the substances which they described as pathological urobilin are mixtures of different substances, and not pure pigments. It is to be noted that the pathological urobilins described by the three writers just mentioned do not agree in their properties, and it is likely that, as suggested by Garrod and Hopkins, the pigments in question were mixtures of normal urobilin with other urinary pigments. While the subject cannot, perhaps, be regarded as finally settled, I strongly incline to the view that the urobilin of jaundice and of other pathological states cannot be distinguished by its physical and chemical properties from the urobilin of the normal urine. The quantity of the pigment in the urine of jaundice may, however, be much in excess of the normal.

On studying the literature relating to jaundice you will meet the view that the substance which has been called hydrobilirubin occurs in the urine during various hepatic disturbances. This pigment, first obtained by Maly through the action of sodium amalgam upon bilirubin, was named to designate the fact that the substance contained more hydrogen and less carbon than bilirubin. Maly believed his hydrobilirubin to be identical with the urobilin which had previously been described by Jaffé, but this view is untenable at the present time, for it appears that hydrobilirubin is either an impure pigment or represents an intermediate stage in the reduction of bilirubin to urobilin.

We cannot feel sure that bilirubin and the excessive urobilin found in the urine in some cases of jaundice are the only pigmentary abnormalities incidental to this pathological state. There is a group of pigmentary substances which resemble urobilin in showing the same absorption band on spectroscopic examination and in exhibiting a brilliant green fluorescence with zinc chloride and ammonia, but which differ from urobilin and from one another in stability and in chemical composition. As yet we know little of the occurrence of these urobilinoid substances in the urine of jaundice.

Bilirubin and urobilin are thus to be regarded as the most important urinary pigments in jaundice. For reasons which I shall explain before the close of the hour the urine sometimes contains bilirubin but no urobilin, or an excess of urobilin without any bilirubin. It has been maintained that there is a special type of jaundice in which urobilin is at no time associated with bilirubin in the urine. The terms 'icterus hæmapheic' and 'urobilin icterus' have been applied to this supposedly special form of jaundice, but numerous observations have demonstrated the fact that, even in those cases of jaundice where excessive urobilin occurs in the urine temporarily unassociated with bilirubin, the pigmentation of the skin and of the serous fluids is due to bilirubin, and not to any form of urobilin.

Before undertaking to explain to you the reasons for the occurrence of urobilinuria in jaundice and other affections of the liver it is necessary for me to refer to the origin of urobilin. A number of hypotheses have been advanced to explain the origin of urobilin and to account for the great variations in the amount observed in the urine. Thus it has

been maintained that in hepatic disease the liver forms urobilin, and that urobilinuria is evidence of disordered function of hepatic cells. Others contend that urobilin is formed in the tissues at large, either by the reduction of bilirubin or more directly from the transformation of hæmoglobin. We have thus an hepatic, a histogenic, and a hæmatogenous theory; but none of these has so much to be said in its favour as the intestinal hypothesis of the origin of urobilin.

The intestinal hypothesis of the origin of urobilin is based on the following well-established facts. In the first place, the amount of urobilin in the fæces (fæcal urobilin or stercobilin) is normally much greater than is to be explained by the amount of urobilin that enters the intestine with the bile. In other words, there is a production of urobilin in the intestine, and chiefly in the large intestine. This urobilin is formed in the intestine at the expense of the bile colouring-matters, and especially bilirubin. If we exclude the bile from the intestine, urobilin is no longer formed. Moreover, when the bile-pigment bilirubin passes rapidly along the intestine, as in certain pathological conditions, urobilin ceases to be formed because there is not sufficient time for the necessary conversion of bilirubin.

The production of urobilin from bilirubin in the intestine appears to be attended by the loss of oxygen on the part of the latter substance. The change is, however, not simply one of reduction, for there is also a loss of nitrogen from the bilirubin molecule.

It is further clear that the change from bilirubin into urobilin is brought about by the action of micro-organisms. When normal bile is inoculated with fæcal matter and kept at the body temperature there is a rapid production of urobilin and a corresponding diminution of the bilirubin. Similar results are obtained where intestinal bacteria that have been isolated and cultivated in bouillon are added to the bile and permitted to grow under anaërobic conditions. Again, the intestinal excreta of newly born infants contain neither bacteria nor urobilin, but after the lapse of about two days urobilin can be obtained in small amounts, and a small number of bacteria appear. Moreover, we can say that in general the greater the intensity of intestinal putrefaction the greater is the formation of fæcal urobilin.

The presence of free alkali appears to be favourable, if

not essential, to the reduction of bilirubin to urobilin by bacteria. Where the stools are acid, as in typhoid fever and in some diarrhœas, there is little or no production of urobilin.

The next point in the intestinal hypothesis of the origin of urobilin to which I wish to call your attention is the relation between the fæcal urobilin and the urobilin of the urine. It has been claimed that the two pigments are not identical, but the careful work of Garrod and Hopkins renders it practically certain that the pigments derived from these two sources are identical in chemical composition. That the fæcal urobilin is absorbed by the intestine and passes into the urine is a well-established fact. The absorption is, however, a slow process, and this accounts for the fact that the fæcal urobilin may be either increased or diminished without immediately affecting the urobilin content of the urine. But after the lapse of a few days the influence of the increased or diminished absorption of the pigment can always be detected. Still the ratio of urinary to fæcal urobilin is exceedingly variable, and we cannot always feel sure that an increased production of pigment in the gut will lead to a correspondingly increased absorption of the urobilin and its reappearance in the urine. Even where absorption takes place the urobilin may be altered in the body to other substances, and in consequence of this the amount of urobilin in the urine may fail to correspond closely to the quantity absorbed from the intestine.

The facts which I have now brought to your notice are sufficient to show how substantial is the foundation on which the intestinal theory of urobilin production has been built. There are, however, certain criticisms which can be made on this theory, and although the time at our disposal does not permit me to discuss these at length, I do not feel justified in omitting all mention of the objections that have been raised. Perhaps the most serious of these objections relates to the connection which certainly exists between hepatic disease and urobilinuria. If urobilinuria be of intestinal origin, how are we to explain the fact that hepatic disease such as cirrhosis and carcinoma almost constantly give rise to urobilinuria? There are two quite distinct ways in which we may endeavour to harmonise the unquestionable influence of hepatic disease with the intestinal origin of urobilin. According to one of these, hepatic disease

influences the excretion of urobilin by giving rise to changes in the quantity and quality of the bile colouring-matters. Conditions like phosphorus poisoning and acute yellow atrophy, in which the secretion of bile-pigment is reduced in amount, would lead to a diminished formation of urobilin in the intestine, and hence to a diminished excretion in the urine. On the other hand, where there is extensive destruction of red blood-cells, as in some anæmias, the amount of bile-pigments is increased, and in consequence we have an increased formation and absorption of urobilin, and hence a urobilinuria. Moreover, different human biles have a different content of bilirubin and biliverdin, and since urobilin is less easily formed from the latter than from the former, we should expect variations in the excretion of urobilin dependent on these qualitative differences.

According to a second view, the liver takes up urobilin after its absorption from the intestine and excretes it in part by the bile and in part converts it into other substances. There is, indeed, good reason to think that the liver-cells are capable of appropriating a certain amount of the absorbed urobilin, but we do not know the fate of this urobilin and cannot say how far the intervention of the liver influences the ultimate excretion of urobilin by the urine. It is not improbable that a recognition of the part played by the changes in the quantity and quality of the bile in liver disease and by the subsequent intervention of the liver-cells after the absorption of urobilin from the gut would help us to understand some facts about urobilin excretion which are not explicable if we consider no other factors than the production of urobilin in the intestine and its absorption and passage into the urine.

I think you are now in a position to understand that we can divide cases of jaundice into three sets of cases, according to variations in the pigments of the urine. We have in the first place those cases of jaundice in which the bile is completely shut off from the gut. In consequence of the great accumulation of bilirubin in the blood there is an intense yellow pigmentation of the skin, and a large amount of bilirubin finds its way into the urine. In these cases there is no urobilin in the urine, because, as I have just explained, this pigment is not formed in the intestine when the bile is excluded from it. The next group of cases comprises those in which there is a partial exclusion of the bile from the

intestine. Enough bile-pigment finds its way into the blood to give rise to slight jaundice and to slight bilirubinuria; but as a large amount of bile passes into the intestine there is an abundant formation of bilirubin, and hence the urine is rich in this pigment. Possibly the increased intestinal putrefaction which always attends even the partial exclusion of the bile from the intestine is concerned with the fact that the excretion of urobilin is increased, in spite of there being less bilirubin for the bacteria to decompose. In the third set of cases almost all of the bile passes into the intestine. Enough, however, gets into the blood to occasion a very slight yellow coloration of the skin, which in some instances can hardly be said to deserve the name of jaundice. The quantity of bilirubin in the blood is so very slight that the pigment does not find its way into the urine in a sufficiently large amount to enable us to detect it. On the other hand, since the quantity of bile-pigment in the intestine is very large, owing either to the outpouring of pent-up bile or to an excessive destruction of red blood-cells, there is formed a large amount of urobilin through the process of reduction by bacteria. The urobilin finds its way into the urine, and causes it to appear strongly pigmented. These are the conditions which exist in certain cases of hæmatohepatogenous jaundice, or after rapid relief to an ordinary obstruction.

Having now considered the effects arising from the deposit of the bile colouring-matters in the tissues, and having reviewed the chief consequences of an impaired secretion of bile as regards the appearance of pigments in the urine, we may take up the functional disturbances in various organs, due to the accumulation of bile-constituents in the blood—that is to say, to cholæmia in the literal sense of the word. A variety of such disturbances occur in the course of jaundice, and some of them find clinical expression in symptoms which go to make up the picture of this pathological state.

There are three constituents of the bile which have to be separately considered in any study of the effects of cholæmia—namely, the bile-acids, the bile colouring-matters, and cholesterin. Let us consider very briefly the chemical character of the bile-acids. The human bile contains at least two kinds of bile-acids—glycocholic and taurocholic—of which the former preponderates. They exist as sodium salts. Both of the bile-acids are the offspring of the same

mother substance—the nitrogen-free cholic or cholalic acid ($C_{24}H_{40}O_5$), a body whose chemical nature is not yet fully known. Cholic acid readily unites with glycocoll and with taurin, and thus forms the basis of glycocholic and taurocholic acid respectively. I need not enter into the chemistry of glycocoll and taurin further than to remind you that both substances are amido-acids—that is, acids containing the amido-group, NH_2. Thus glycocoll is simply amido-acetic acid, $CH_2.NH_2.COOH$, while taurin has the more complex constitution of amido-ethyl-sulphonic acid, $SO_2\begin{matrix}C_2H_4.NH_2\\CH\end{matrix}$ and contains sulphur. We know nothing definite as to the origin of cholic acid in the body. Glycocoll is yielded by the decomposition of proteids. Taurin is also thought to be derived from proteid, perhaps from the proteid of the food.

An adult human being usually produces from eight to twelve grams of bile-salts daily, or, to speak more accurately, excretes or secretes this quantity in the bile; since, as you are aware, the peculiar circulation of the bile-salts makes it unnecessary for the liver to actually produce daily so large a quantity as passes into the bile, the bile-salts being absorbed from the intestine to pass again into the bile. Now, in conditions of jaundice the quantity of the bile-salts which finds its way into the urine is very small. This behaviour on the part of the bile-salts is in sharp contrast to that of the bile-pigments, which, as we have just seen, are much increased. Indeed, it is only during the first few days of jaundice that the bile-salts can be detected in the urine. After that they disappear entirely.

There are three possible explanations of the fact that the bile-salts in the urine of jaundice are diminished or absent. One is that there occurs an excessive accumulation of these salts in the blood and tissues. There are two obvious objections to such a view. In the first place, the accumulation of the bile-salts would cause much more marked symptoms of poisoning than we actually find in jaundice. There is, indeed, a small accumulation of bile-salts in the blood, but it is not sufficient to be explained on the view that the bile-salts are formed as in health, and are stored in the blood like the bile-pigments. In the second place, it is quite clear that an accumulation of bile-salts in considerable amount in the blood would lead to their appearance in the urine in far greater amount than they are actually found.

A second explanation of the disappearance of the bile-salts from the urine is that they are destroyed in the blood and thus rendered harmless. This view has been advanced by eminent physiological chemists, but is open to the great objection that bile-salts injected into the blood reappear in the bile.

The only remaining possibility is that the bile-salts are produced in diminished amount in the course of jaundice. There are a number of reasons which indicate that this is the only tenable explanation of the appearance of the bile-salts in the urine in such small quantities. The most direct evidence bearing on this question comes from analyses on the human subject which show that the bile excreted in jaundice contains only a very small percentage of the bile-salts. Thus in one case the bile contained fifty-five thousandths (0·055) per cent. of sodium taurocholate and one hundred and sixty-five thousandths (0·165) per cent. of sodium glycocholate. When one recalls that the normal percentage of the bile-salts in the bile is about two per cent. it is easy to see how great a decline in the manufacture of the bile-salts occurs in jaundice. We are certainly justified in concluding that in jaundice the liver-cells lose the capacity to manufacture bile-salts in anything like the normal amount. In view of the fact that bile-acids possess very definite toxic properties this is a most fortunate circumstance.

Let us now consider these toxic properties of the bile-acids. If we add a solution of the bile-salts to blood in a test tube, we can readily convince ourselves that they have the power to dissolve the red blood-cells. We might jump to the conclusion that in jaundice the bile-salts have a similar destructive influence on the red blood-cells. There is, however, very good evidence that these bile-salts never exist in the blood of jaundice in sufficient concentration to exert a destructive action upon the red cells. Moreover, if such an action occurred we should see very definite clinical indications of it. We should expect to find, at least sometimes, that hæmoglobinuria is present at the onset of jaundice, since, as I have already pointed out to you, a marked and rapid destruction of red cells leads to the appearance of hæmoglobin. As a matter of fact we do not encounter hæmoglobinuria at the onset of jaundice except in conditions where we have good reason to think that the disturbance of the blood is the primary condition; as, for example, in

malarial poisoning, in poisoning by toluylendiamin, &c. Then, again, we should certainly be justified in believing that anæmia would result from any considerable and prolonged destruction of red cells, due to the action of bile-salts in the blood. But the fact is that anæmia is not a feature even of the most pronounced obstructive jaundice. We are thus obliged to conclude that the bile-salts never occur in sufficient concentration in the blood to occasion a destruction of its formed elements.

I do not know of any systematic study of the influence of the bile-salts upon the coagulation of the blood. There are, however, some clinical observations which show that in jaundice the coagulation time of the blood may be lengthened by many minutes. A distinct inclination to hæmorrhage after operation has been noted in many cases of jaundice, possibly in one-third of the cases in which operative measures have been undertaken. Even spontaneous hæmorrhage has been seen to follow the absorption of bile-constituents, as in a case where after rupture of the gall-bladder the bile passed into the peritoneal cavity. This disposition to hæmorrhage is probably to be referred to impaired power of coagulation, although some writers have suggested that it arises from alterations in the walls of the smaller blood-vessels. The delay in coagulation that occurs in at least some instances of jaundice is not improbably due to the action of the bile-salts, but positive evidence of this appears to be wanting, and we cannot be sure that other constituents of the bile do not play a part.

Practitioners have long been familiar with the slowing of the pulse which is such a common phenomenon in jaundice, especially during the first few days of ordinary obstructive jaundice unattended by fever. Nearly forty years have passed since Röhrig observed that the bile-salts are capable of slowing the heart action, and made the inference that in jaundice the slow heart is due to their action. He thought the bile-salts acted directly on the heart muscles or on the cardiac ganglia, and this view gained wide acceptance. Recently evidence has accumulated which renders it extremely probable that the bile-salts exert an inhibitory action on the vagus nerve. Among the indications in favour of this view is the fact that in some instances at least the slow heart of jaundice can be accelerated by the use of atropine, which, as you are aware, has a paralytic action in the vagus.

You may have observed that the slow pulse of jaundice is usually large, soft, and dicrotic, whereas most slow pulses show a fair or excessive degree of tension. This condition of the pulse points to a paralytic effect of the bile-salts on the blood-vessels. It is possible that the slight depression of temperature which we notice in many persons with jaundice is dependent on this widening of the peripheral blood-vessels.

Numerous experimental studies have been made on the effects of the bile-salts on the nervous system, but the results are by no means concordant. While some writers have described the most pronounced irritative phenomena, such as tetanic and clonic convulsions, others have entirely failed to produce these effects. These divergent results are probably to be referred to differences in the experimental methods of the various workers. In rabbits the direct application of a solution of bile-salts beneath the dura certainly occasions very decided irritative phenomena, much resembling those produced by strychnia poisoning; but we have no justification whatever for supposing that results like these can help us to understand the effect on the nervous system of the human subject arising from the presence of the bile-salts in the blood in jaundice. The most reliable observations show that subcutaneous and intravenous injections of the bile-salts cause depression and coma. Small doses in animals give rise to muscular weakness.

Upon the whole the balance of evidence is to the effect that the slighter nervous phenomena of jaundice, headache, psychical confusion, general prostration, and slowing of the heart are due to the action of the bile-salts. This view seems to accord well with the fact that these symptoms exist as a rule only during the first days of jaundice; that is to say, at a time when the bile-salts are most abundant in the blood. There is no basis whatever for the contention that the more serious nervous symptoms of the severe form of jaundice which we call *icterus gravis* are due to the influence of the bile-salts in the blood. Indeed there is satisfactory evidence that the concentration of these salts is quite insufficient to occasion delirium, convulsions, or coma. It is far more likely that bacterial poisons or other toxic substances are responsible for these obtrusive nervous phenomena.

Another clinical manifestation that has been attributed to the action of the bile-salts is the albuminuria noted in

many instances of jaundice. It has also been supposed that casts may be attributed to the same influence. When we come to examine the evidence on which this view is based we find it to be of a flimsy character. It is true that the subcutaneous injection of bile-salts in animals has been found to produce degenerative changes in the epithelia of the urinary tubules, together with cast formation. It is necessary, however, to be extremely cautious about transferring these results to man. Moreover the alterations in the renal epithelium which have been described in cases of jaundice accompanying acute yellow atrophy, phosphorus poisoning, carcinoma of the liver, and cirrhosis of the liver, seem more likely to be the result of other toxic agents than the bile-salts. As for the group of cases in which jaundice is most frequently accompanied with renal lesions—that is to say, cases of infectious jaundice—we can feel confident that the indications of renal disease are in reality due to the micro-organisms concerned with the infection, through the agency of their products.

Recent studies have shown that even the thyroid gland is not exempt from the influence of the toxæmia of jaundice. Thus it was found that the lymph spaces of the thyroid were much distended with colloid secretion in a series of patients with jaundice. It has been inferred that the toxæmia of jaundice stimulates very markedly the thyroid secretion, and it has been suggested that this over-stimulation of the thyroid secretion is antitoxic in character and adapted to neutralise the action of the bile-salts. But we must not forget that it is by no means demonstrated that this effect upon the thyroid can really be referred to the bile-salts.

Until recently the bile colouring-matters have not been made responsible for any of the phenomena of jaundice except the yellow coloration and dryness of the skin, the occurence of itching, and the peculiar disturbance of vision called xanthopsia. Indeed, even itching and xanthopsia have been referred by some writers to the action of the bile-salts. The truth is that we are quite in the dark as to the cause of the general itching of the skin so often noticed in the course of icterus. It has been noticed that this symptom sometimes develops a considerable period before the yellow coloration of jaundice appears. You can readily see that this fact, which is well authenticated, is a most serious objection to the view that the itching is due to the deposit

of bile-pigment. It is possible that the symptom depends on the presence of some constituent of the blood of which we are entirely ignorant at present. But I am disposed to think we need not look so far for an explanation. The skin of jaundiced persons is apt to be very dry, and this is, perhaps, the real cause of the itching.

The xanthopsia, or yellow vision of jaundice, has been referred to the impregnation of the ocular media and retina with the bile-pigments. The presence of these pigments is thought to occasion the absorption of the blue and violet rays of light. Such absorption, as you can easily understand, would fully account for the presence of the blue and violet blindness noted in the early stages of some cases of jaundice. A serious difficulty with the view which ascribes xanthopsia to the bile-pigments is the clinical observation that this symptom may occur where jaundice is slight, or be absent where it is profound. Thus you perceive we are in ignorance as to the nature of this symptom also.

According to some observers, the bile colouring-matters are responsible for more serious disturbances than those I have just described. They believe that the bilirubin of the bile is even more poisonous than the bile-salts, especially in its effect on the heart, kidneys, and the nervous system. An examination of the evidence bearing on this subject leads me to think that these conclusions are based on faulty experimental observations. More carefully conducted observations show that the poisonous action of bilirubin is really very slight, and we are certainly not justified at the present time in attributing more effects to its presence than those I have already mentioned. I do not feel, however, that we can regard the matter as settled.

The third constituent of the bile to which writers have attributed toxic activity is cholesterin. This substance, you remember, is a monatomic alcohol, with the composition represented by the formula ($C_{26}H_{43}.OH$). It is usually present in the bile of the gall-bladder in a proportion varying from 0·1 to 1 per cent. The severe symptoms of *icterus gravis* have been referred by some observers to cholesterin; but the experiments on which this view is based are quite unreliable. The toxic results obtained were clearly due to the fact that in certain experiments the cholesterin, being introduced into the blood imperfectly dissolved, gave rise to fatal emboli. In other experiments the toxic effects are

clearly due to the glycerine which was mixed with the cholesterin. I have touched on these observations more fully than I should have done were it not that they afford an excellent example of the sources of error that exist for experimenters, especially for those engaged in determining the toxic properties of individual constituents of the blood. It has been shown that cholesterin is in reality entirely devoid of toxic properties.

Before taking leave of the subject with which we have just been engaged—namely, the effect upon the organism of the toxæmia of jaundice—I wish to say a word as to the influence which this toxæmia exerts upon general metabolism in ordinary obstructive jaundice. It has been thought that the bile-salts are capable of acting as protoplasmic poisons, and of occasioning an increased destruction of tissue. There appears, however, to be no substantial evidence in support of the view that such a disturbance in proteid metabolism occurs in man. The output of urea has not been shown to be greater in human obstructive jaundice than is the case in a condition of health where an equal amount of food-material is absorbed from the gut. There are, indeed, some observations on dogs in which the bile-ducts have been ligated that indicate the occurrence of excessive proteid waste ; but it is impossible to say whether these results are in any sense applicable to human obstructive jaundice. In the case of the toxæmic form of jaundice, due to infectious disease, it is likely that we have to take account of the existence of a protoplasmic poison, which causes an excessive destruction of proteids in the body, and a correspondingly increased elimination of nitrogen. But, of course, cases of this type belong to an entirely different category from those in which the toxæmia is due to the simple accumulation of biliary constituents in the blood.

We may now consider very briefly certain consequences of an exclusion of the bile from the intestine. These effects are chiefly of three kinds : first, the defective absorption of fats ; second, the increase of intestinal putrefaction ; and third, a loss of fæcal colouring-matter. As we have already discussed this subject in another relation, I shall merely remind you of the more important facts connected with these intestinal disturbances. You will recall that the chief influence of withholding the bile from the intestine is the

impaired absorption of fats. The process of fat-splitting goes on very much as it does in health, owing to the presence of the pancreatic ferment. Where the pancreatic juice is also excluded the impairment in fat absorption is much greater, and there may be a markedly diminished decomposition of neutral fat. The fat lost by the fæces in cases of catarrhal jaundice is intimately mixed with the other constituents of the fæces, and contributes to impart a peculiar light grey colour and salve-like consistence to the movements. On microscopical examination we find that the fæces contain an abundance of needle-shaped crystals often arranged radially. These crystals were at one time erroneously supposed to consist of tyrosin. They are now known to be sodium calcium or magnesium salts of the higher fatty acids. Crystals of free fatty acids are sometimes abundant in the stools of persons with jaundice, and under these circumstances the fæces have a peculiar silvery lustre.

There is another important effect of impaired absorption of fats which I must not omit to mention. This is the loss of weight that occurs in almost every case of jaundice. If the patient were capable of taking an increased supply of carbohydrates and proteids, this deficiency could be readily compensated. The appetite, however, is poor, and the patient does not assimilate enough food material to enable him to keep up his caloric expenditure without drawing upon his own fats and proteids. In consequence of thus drawing upon his own tissues the patient loses weight.

The second important effect of excluding the bile from the intestine is the increase of intestinal putrefaction which we observe. You will remember that I told you the bile performs the important function of hurrying the food along the digestive tract, and of thus preventing that stagnation of the intestinal contents which regularly leads to increased proteid decomposition. The excessive putrefaction that follows the exclusion of the bile from the intestine during obstructive jaundice is shown clearly by the increase of ethereal sulphates. Sometimes the indican reaction of the urine grows very strong, and frequently the quantity of phenol and aromatic oxy-acids is much increased. Whether under these circumstances there are produced any important putrefactive substances at present unknown to us I cannot, of course, venture to say. I admit that I am strongly inclined to believe that some of the slighter nervous symptoms

observed in the course of obstructive jaundice, as, for example, headache, are in reality due to the absorption of excessive putrefactive products, rather than to the existence of a cholæmia.

It has been suggested that excessive intestinal putrefaction is distinctly promoted by the presence of a marked excess of fat in the intestine, and I am inclined to favour this idea. It is easy to see how the intimate admixture of an excessive quantity of fat with proteid material in the intestine might greatly hinder, in a mechanical way, the absorption of proteid food. Such a hindrance would naturally give the micro-organisms of the intestine a highly favourable opportunity to break up the proteid substances.

The complete diversion of the bile from the intestine gives to the fæces a light grey or slaty tint dependent on the absence of the chief colouring-matter, urobilin. If the fæces under these circumstances be extracted with alcohol, they no longer impart to it the reddish colour due to the presence of urobilin. The absence of urobilin is the result of the absence of bilirubin and biliverdin from the gut, and the cause of the absence of urobilin from the urine. But, as I have already said, urobilin is formed in the gut and reaches the urine where even small amounts of bile still enter the intestine.

We have now discussed the leading features in the pathological chemistry of jaundice. Perhaps it will aid you if I summarise the points which I wish most strongly to impress on your memory. In the first place, we have to draw a fairly sharp line between the cases of jaundice dependent on mechanical obstruction in the larger ducts and those cases in which the obstruction occurs chiefly in the smallest bile-ducts, and is the consequence of the activity of toxic substances which have led to a marked increase in the destruction of red blood-cells. In the first form of jaundice the alterations in the composition of the blood are dependent upon the accumulation of the bile constituents—namely, the bile-pigments and the bile-salts. In the second group of cases—those of toxæmic jaundice—these bile-constituents are present, but are of less importance to the organism than those poisons, usually the product of bacterial activity, which give rise to the excessive blood destruction. In the cases of ordinary obstructive jaundice the bile is very frequently shut off completely from the intestine, in

consequence of which the fæces assume the grey colour due to impaired fat absorption, and usually a disgusting odour due to the excessive putrefaction of proteids. In the toxæmic form of jaundice, on the other hand, there is seldom a complete withdrawal of the bile from the intestine. In fact, the quantity secreted may be much in excess of what is normal, owing to the greatly increased formation of bile-pigments, which is the consequence of excessive destruction of red blood-cells. The fæces in these cases are coloured brown from the excess of bile-pigments or polychromia. In the urine, too, we see differences in the two sets of cases. In complete obstructive jaundice the urine contains a large amount of bilirubin but no urobilin. In the cases of toxæmic jaundice enough bile soon reaches the intestine to give rise to the appearance of urobilin in the urine, and the quantity of bilirubin is not so large as in cases where the obstruction is complete. The bile-salts are somewhat more abundant in the urine in obstructive than in toxæmic jaundice during the first few days, but after this they are absent from the urine in both sets of cases.

There are also clinical differences between the simple obstructive and the toxæmic types of jaundice. In the first there is little or no fever, or even a subnormal temperature, and nervous symptoms are not pronounced even though the patient be intensely jaundiced. In the second form of jaundice there is usually a rise in temperature due to the action of bacterial poisons, and the jaundice is frequently slight, although cerebral symptoms arevery of ten obtrusive.

I have probably given you the idea that the obstructive and toxæmic forms of jaundice are always readily distinguishable, for in my description I have had in mind mainly the marked types of the disorder. In practice, however, we sometimes meet cases where the elements of both types are combined. It is of the utmost importance that you should learn to make the correct diagnosis of the cause of jaundice, a diagnostic problem not always easy to solve and one worthy of your closest study. The practical importance of this diagnosis is so great because of its bearing upon the choice of the correct treatment, which, as you are aware, is often surgical in character. It is well to bear in mind that although catarrhal jaundice—that is, jaundice connected with gastro-duodenitis—is the commonest form of the condition, the obstruction which underlies the jaundice is often

dependent on malignant disease, compressing the common bile-duct. Then, again, there are cases of jaundice connected with disease of the gall-bladder, not necessarily involving the presence of gall-stones, but dependent on inflammation of the gall-bladder itself.

You are, of course, aware that the treatment of jaundice depends upon the cause. In cases of gall-bladder disease, or of pressure upon the larger bile-ducts by tumours, we have to resort to surgical interference. The cases of jaundice due to toxæmia can only be treated indirectly through measures addressed to the primary infectious disease. The treatment of cases of obstructive jaundice of the simple catarrhal variety due to gastro-duodenitis requires some mention here. You know that these cases run a course which differs much in different instances. We do not know just why it is that some of these patients recover in the course of a few days, although we may do nothing in the way of treatment, while other cases persist for many months in spite of all we do. The slighter cases can hardly be said to require any treatment except the use of a milk diet. Nevertheless, since we are unable to say at the outset whether a case is likely to run a short or a long course, it is well to do everything we can from the outset in the way of treatment. My conviction is that the most important thing for us to do is to diminish the gastritis and duodenitis on which these cases of jaundice appear to depend. It is therefore essential that we should remove all causes of irritation to the mucous membrane of the stomach and duodenum. A strict milk diet for a week or ten days is very helpful in this connection. The milk should be ordinary skimmed milk containing only about 1 per cent. of fat. The advantage of excluding the milk fat in this way lies in the circumstance that fat absorption is greatly diminished in jaundice, and that it is unwise to load the intestine with food which is absorbed only in limited amount. As I have already mentioned, the presence of fat in abundance probably favours excessive proteid putrefaction, a thing which we should endeavour to limit as far as possible. After five or six days on a diet of skimmed milk the patient may be permitted to take broths of chicken or mutton in addition to milk, and may be allowed a moderate quantity of carbohydrate food in the form of finely divided and thoroughly cooked cereals, such as hominy, rice, or wheatena. I think it is distinctly advantageous to

practise stomach washing once a day regularly in these cases, even in the mild ones, since it is very helpful in quieting the indications of gastritis. Even in cases where you do not find any of the classical symptoms of chronic or subacute gastro-duodenitis I think it desirable to practise lavage. Many physicians also make use of cathartic drugs, but I am of the opinion that if we employ drugs to relieve the constipation which almost always exists in patients with catarrhal jaundice who are on a milk diet, we should be cautious in avoiding laxatives that possess an irritant action. I should therefore advise you not to employ cathartic salts, but to use calomel in small repeated doses. It may, perhaps, suggest itself to you that the absorption of fats would be aided by giving moderate doses of bile-salts or of ox-bile. You will remember, however, that I told you the bile-salts are a powerful stimulus to the liver-cells. If, therefore, we give the bile-salts for the purpose of improving the fat absorption, these salts will be absorbed and will stimulate the liver to increased activity in the formation of bile. Since there is an obstruction to the escape of the bile, it seems unwise to do anything which will stimulate the production of bile while this obstruction persists. The use of cold-water enemas has been recommended in jaundice in the belief that it in some way favours the relaxation of the obstructed bile-ducts. I have tried the method in many cases, but have not been able to convince myself that it is really serviceable.

The first indication of improvement in cases of catarrhal jaundice is often a diminution in the amount of bile-pigments in the urine and the reappearance of some bile-pigment in the fæces. When you observe these signs in the course of catarrhal jaundice you can feel confident that your patient will before long show a diminution in the intensity of the pigmentation of the skin.

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LECTURE XI

THE CHEMICAL PATHOLOGY OF HEPATIC DISEASE (*continued*).

Derangements of hepatic function distinct from disorders in the production of bile—Assumption that the excretion of urea is diminished in hepatic disease owing to inability of the liver-cells to form sufficient urea—Grounds for the view that the liver is largely concerned with the production of urea—Conversion of the amido-acids into urea in the isolated mammalian liver—Formation of urea from ammonium salts—Consequences of establishing an Eck fistula—Decreased excretion of urea in acute yellow atrophy, poisoning by phosphorus, and hepatic cirrhosis—Increased excretion of ammonia in these conditions—Acid intoxication as a probable cause of excessive excretion of ammonia and diminished excretion of urea—Relation of the liver to the production of uric acid—Occurrence of leucin and tyrosin in the urine in hepatic disease—Relation of albumosuria to hepatic disease—The glycogenic function of the liver—Disturbances of this function—Conditions attended with diminished storage of hepatic glycogen—The antitoxic function of the liver—Action of the liver on alkaloids; on metals and metalloids—Action on digestive products—Nature of the processes involved in detoxication—Action of the liver on bacteria—Effects of partial or complete elimination of hepatic function—The toxicity of the urine as evidence of toxæmia—Therapeutic indications in cases of hepatic disease attended by slow destruction of cells.

At our last meeting I endeavoured to sketch for you some of the prominent phenomena connected with disturbances of the most obvious functions of the liver, namely, the production of the bile. In doing this I found it convenient to group the facts relating to disordered formation and secretion of the bile around the condition which we call jaundice. This morning I invite your attention to a very different class of derangements—derangements connected with functions of the liver distinct from bile-formation. You are, of course, well aware that the cells of the liver are capable of doing many kinds of work besides that which leads to the production of bile, and that the hepatic cells are perhaps the most versatile of any in the body. Thus, as I mentioned in the last lecture, they

form and store glycogen, convert ammonium salts into urea, carry on processes of oxidation with intense activity, and exert a remarkable power of destroying or modifying toxic substances, a function closely connected with these active processes of oxidation and synthesis. While we are still very far from a satisfactory understanding of these varied functions, we have, nevertheless, accumulated enough knowledge to justify the conviction that these more obscure cellular activities are of the utmost importance for the maintenance of health, and that their disturbance means disease.

I may conveniently group the facts which I shall bring before you to-day into three classes: (1) Those relating to disturbances in the ability of the liver-cells to carry on processes connected with nitrogenous metabolism; (2) those relating to disturbances in the glycogenic functions of the liver-cells; (3) those connected with the failure of the hepatic cells to normally carry on their power to convert or destroy toxic substances. The first and third classes overlap one another largely, but I think it best to keep them distinct in what I have to tell you.

The liver has long been suspected of playing a leading part in the production of the chief representative of the proteid waste of the organism, urea. This belief was grounded on the observation that there are certain diseases of the liver in which the excretion of urea in the urine is much below the normal quantity. The diseases in which this diminished excretion of urea was observed are conditions like cirrhosis of the liver and acute yellow atrophy, in which we know the liver-cells to be extensively damaged. What could be more natural than to regard the diminution in urea as a consequence of this destruction of liver-cells, and to assume that the extent of this destruction could be measured by keeping watch of the amount of urea passed in the urine? These suppositions have been current for many years in spite of the fact that they rest on observations which were in many instances technically incorrect. It is only in recent years that these views have been scrutinised with the aid of scientific methods of investigation.

The doctrine that the urea excretion falls off in hepatic disease because the liver-cells are no longer able to make sufficient urea really involved three distinct propositions.

These are, first, that the liver is an important seat of urea formation; second, that there is often a decrease in the excretion of urea in diseases that cause destruction of liver cells; and third, that any decrease in the excretion of urea observed in the course of liver disease depends upon the inability of the hepatic cells to make urea. The first and second of these propositions we shall find to be correct; the third is erroneous. Let us examine them in turn.

Modern research has placed us in possession of facts which leave no doubt that the liver is very largely concerned in the formation of urea. Perhaps the most direct evidence that we possess on this subject comes from experiments upon the isolated mammalian liver, in which it is possible to keep up an artificial circulation of blood. You can readily understand that in a cleverly devised experiment the conditions might be kept favourable for the continued activity of the liver-cells in carrying on some of their chemical functions, as, for instance, the function of forming urea from substances suspected of being convertible into urea. You will remember that urea is, chemically speaking, the amide of carbonic acid or carbamide, $CO(NH_2)_2$, each molecule of which contains two groups of NH_2. It would not be singular if the liver were capable of converting into urea substances which contain the NH_2 groups, and investigators have made use of such substances in their experiments to determine the origin of urea. Among the substances which contain the NH_2 group are those known as the amido-acids, for example, glycocoll, which is amido-acetic acid ($CH_2NH_2.COOH$), and *a* - amido - isobutyl - acetic acid ($(CH_3)_2CH.CH_2.CH(NH_2).COOH$, which is leucin. Now it is a fact that either of these amido-acids, glycocoll or leucin, is transformed into urea in the liver if introduced into an isolated mammalian liver in the blood-stream of an experimental circulation. That such a conversion actually occurs under these conditions is shown by the fact that the amido-acids leaving the liver are much less in amount than the quantity introduced, while, on the other hand, the quantity of urea which leaves the liver is correspondingly increased. It is not my wish to give you the idea that the liver ordinarily manufactures its urea chiefly from amido-acids like glycocoll

and leucin. It is true that a certain proportion of the urea excreted by the urine is made from amido-acids which enter the liver after they are absorbed from the digestive tract, where, as you are well aware, a part of the proteid food may be converted into amido-compounds. I have given you this particular example of urea formation in the liver because we possess such very direct evidence in regard to it. There is good reason to believe that the liver ordinarily produces its urea very largely in another way, namely, by the rearrangement or conversion of ammonium salts.

It is well known that when certain salts of ammonia are introduced into the blood of a mammal, a portion at least of the ammonia fails to make its appearance in the urine, while the urea in the urine is correspondingly increased. This fact of course proves nothing as to the part which the liver takes in effecting the increase of urea noted under these circumstances; it shows merely that ammonia in certain combinations is somewhere in the body changed into urea. We are able, however, to supplement this information in a way which indicates that the liver is concerned with the conversion of ammonia into urea.

Perhaps you remember my telling you in a previous lecture that the proteids in the intestinal tract yield ammonia as one of the regular accompaniments of an intestinal digestion. We do not know just how this ammonia arises. Probably it is split off by the epithelial cells of the stomach and intestine and pancreas during their glandular activity, and especially during the absorption of proteid food. However this may be, we know that during digestion the blood of the mesenteric and portal veins is very much richer in ammonia than the arterial blood generally. We know further, that the blood which leaves the liver contains no more ammonia than the arterial blood which passes to the intestine, or, to state it differently, the blood of the portal vein on passing through the liver loses its excess of ammonia. The inference that this excess of ammonia is converted into urea is fully justified. It has been calculated for one particular experiment that the liver of a dog weighing 9·5 kilos. received 5·497 grams of NH_3, and lost only 2·332 grams of NH_3, 3·165 grams of NH_3 having been converted in the liver into urea. The amount of NH_3 thus converted is equal to 5·58 grams of urea for the twenty-four hours.

But this is by no means all the evidence we have as to

the origin of urea in the liver. We possess important evidence of a negative kind derived from the highly interesting observations that have been made upon dogs, in which an Eck fistula has been produced. Probably you do not know that an Eck fistula is made by establishing a connection between the portal vein and the inferior vena cava, by which the blood from the intestinal area passes directly into the right heart without first traversing the liver. By means of this procedure the liver is excluded from performing its functions, and we are thus in a position to study what happens when these functions are eliminated by experimental means. The operation is, of course, a formidable one, and, even when entirely successful from a surgical standpoint, leads to the death of the dog in twenty-four hours or less. But during this short period of life without a liver the quartet of German and Russian investigators—Hahn, Massen, Nencki, and Pawlow—succeeded in making observations of the highest importance in connection with the topic we are discussing. They found that the content of NH_3 in the urine is very strikingly increased after the establishment of the Eck fistula, and that there is a proportionate diminution in the excretion of urea. This is precisely the result we should expect in case the liver were concerned with the formation of urea, and, taken in connection with the facts which I have already brought to your notice, it goes far to establish the doctrine that the liver is an important seat of urea formation.

I do not intend giving you the idea that no urea is formed after the establishment of the Eck operation. Urea continues to be produced in large amount; and, indeed, we cannot conceive that life could be even temporarily maintained without the continuance of this very fundamental chemical activity. There is, however, a sufficient accumulation of an ammonia compound to bring on death before many hours have passed.

It will probably occur to you that the liver evidently does not have exclusive control of the formation of urea, and that other cells than those of the liver must be concerned in carrying on this particular form of work. This is a conclusion which there is every reason to regard as correct, for the continued appearance of large quantities of urea in the urine after the experimental elimination of the liver can only mean that other organs are carrying on the function of

making urea. It would, indeed, be a singular thing if one organ should have a monopoly of so fundamental and vital a process as that of manufacturing urea. It is probable that all the parenchymatous organs and the muscles share the urea-forming function with the liver, but in a lesser degree.

We may thus affirm the correctness of our first proposition, since it is evident that the liver normally makes urea in large amounts, though not to the exclusion of other organs. We do not know how large a proportion of the total urea is produced in the liver; possibly it is not very far from one-half.

We do not know just how the liver-cells manufacture urea, but there is reason to believe the act to be synthetic in character, and involving the union of ammonia and carbonic acid. It is thought that the formation of ammonium carbonate ($CO(NH_4)_4$) is a preliminary stage in the production of urea, but it is uncertain whether the molecule of ammonium carbonate is converted directly into urea, or whether there is an intermediate formation of ammonium carbamate $\left(CO\begin{matrix}NH_2\\ \diagdown\\ \diagup\\ CO.O.NH_4\end{matrix}\right)$

The latter view has been strongly maintained by some investigators, but I do not consider the evidence convincing. The nervous symptoms—somnolence, ataxia, convulsions, and coma—which develop after the Eck fistula has been established have been attributed to the action of ammonium carbamate on the central nervous system, but may with equal propriety be referred to the presence of ammonium carbonate. The truth is, we simply know that there is an excess of ammonia in the blood after formation of an Eck fistula. We do not know in what form the ammonia exists.

I have referred once or twice to the fact that certain salts of ammonia undergo conversion into urea. It is proper that I should explain to you the nature of these salts. It is only those combinations of ammonia with a readily oxidisable acid or with carbonic acid that can be converted into urea. The ammonium salts of a mineral acid, as, for instance, ammonium chloride or ammonium sulphate, are not available for the synthesis of urea.

We can now examine the second proposition of which I spoke at the beginning of the lecture, namely, that there is

actually a decrease in the excretion of urea in diseases which occasion extensive destruction of liver-cells. Such diseases include the acute destruction of liver-cells observed in acute yellow atrophy and phosphorus poisoning, and also some instances of chronic damage to the hepatic cells in the course of interstitial cirrhosis of the liver and in fatty liver.

What knowledge we have on this subject is inferential and indirect rather than positive. It is well known that in the diseases of the liver, to which I have just referred, the urine frequently contains a much larger percentage of nitrogen of ammonia than is observed in health. In a normal human adult the urine contains from 2 to 5 per cent. of its nitrogen in the form of ammonia, about 2 per cent. of uric acid, and from 3 to 5 per cent. in the form of extractives and nitrogenous compounds closely related to uric acid. The remaining nitrogen of the urine is present as urea. In the various diseases of the liver, accompanied by extensive damage to the liver-cells, the increase in the nitrogen of ammonium is often pronounced. Thus in acute yellow atrophy so large a proportion of nitrogen of ammonia as 17·3 per cent. was found in one case. In one instance of human poisoning by phosphorus the nitrogen of ammonia amounted to 18 per cent., in another to 25·8 per cent. In dogs poisoned by phosphorus similar results have been obtained. In cirrhosis of the liver with great atrophy of liver-cells the nitrogen of ammonia may reach 20 per cent. of the total nitrogen of the urine. I have myself observed examples of cirrhosis in which the nitrogen of ammonia was almost as high, but must hasten to say that in many cases of cirrhosis the excretion of ammonia is normal. In persons with advanced fatty livers and marasmus, especially in infancy, the nitrogen of ammonia may reach 10 per cent. or more of the total nitrogen. It seems to me there is only one interpretation to be placed on these results, namely, that the increased excretion of ammonia occurs at the expense of urea. If this is not the case, whence does the nitrogen of ammonia come? There is satisfactory evidence that it does not come from the extractive nitrogen or the uric acid, since the nitrogen in this form is not materially reduced. We know that in health the ammonia which reaches the liver by the portal vein is converted into urea. It is also certain that the ammonia formed in the muscles and elsewhere in the course of normal metabolism is converted into urea. In

fact only a very small proportion of the ammonia which is formed in the healthy body fails to be made up into urea. If, now, we find that the ammonia in the urine is very largely increased in disease, whether it be disease of the liver or of some other organ, we are forced to conclude that this ammonia represents ammonia that should in the normal course of events have been changed into urea. In other words, we may answer our second proposition in the affirmative, and say that in some diseases of the liver which are accompanied by an increased excretion of ammonia by the urine, there is a proportional diminution in the formation of urea. It would be interesting to have more direct evidence on this point; that is to say, evidence derived from a study of the metabolism of patients in nitrogenous equilibrium; but so far as I am aware such studies undertaken with the view to clearing up the question under discussion are at present wanting. But, as just intimated, I consider the indirect evidence I have brought to your notice as sufficient to enable us to reach a conclusion.

We are now in a position to examine the third proposition bearing on the question of urea formation in liver disease, namely, that any decrease in urea excretion observed in hepatic disease depends on the inability of the hepatic cells to make urea. As I have already remarked, this view has been rather widely accepted without much question, and it is important that we should have definite knowledge as to its correctness.

Perhaps you will ask whether there is any alternative to the proposition that, where urea formation is diminished in liver disease, this depression of function is due to a failure in the capacity of the hepatic cells to make urea. If this question has suggested itself, you can safely answer it affirmatively, for it is certain that an increase in the nitrogen of ammonia of the urine by no means proves the liver unable to make the normal amount of urea owing to a failure in the synthetic functions of its cells. It merely indicates that urea is not formed in full amount because a certain quantity of ammonia, which would ordinarily go to form urea, is diverted for a very different purpose, namely, that of neutralising an acid. If you can recall the lecture in which I described for you some of the leading chemical defences of the organism against disease, you will remember

that I mentioned the power of neutralising acids as one of the most important of chemical defences. I told you something of the conditions under which the ammonia of the body is employed to neutralise foreign acids or physiological acids imperfectly burned, and which threaten to reduce the alkalescence of the blood. Now we know that in phosphorus poisoning, in acute yellow atrophy, and in some instances of cirrhosis of the liver, the ammonia which appears in the urine is linked to lactic acid. The same thing is true of the ammonia which appears in the urine of dogs after making an Eck fistula. We do not know the nature of the acid in all cases of liver disease where the excretion of ammonia is increased, but in many instances, at least, the acid is that variety of lactic acid which is formed in the muscles and is known as sarco-lactic acid to distinguish it from the lactic acid formed in the course of fermentation. Although we do not know the chemical nature of the acid to which the ammonia is tied in liver disease, we can be certain that an organic acid exists in excessive amount whenever the nitrogen of ammonia in the urine is augmented. We may assume that the acid is either formed in excess or is not normally utilised and burned. In either case it would unite with a base in the body to be ultimately excreted by the urine. Is it not likely that this is what actually occurs in those cases of liver disease in which the ammonia of the urine is increased? If so, any diminution in urea might be due to the diversion of the ammonia of the tissues rather than to failure of the liver-cells in their ability to carry on their full production of urea. I trust I have made clear to you the difference between a diminished formation of urea owing to this diversion of ammonia and the diminished production of urea that may possibly occur because the liver-cells have lost their power of effecting a synthesis of its constituents.

But you will naturally object that this interpretation of the diminution in urea represents merely a possibility. Is there no evidence of a more positive character bearing upon the question whether the urea-forming function of the liver is undisturbed in cases where the excretion of ammonia is increased, and that of urea diminished? We are fortunately acquainted with observations which have a direct bearing on this question. An enterprising German investigator, Weintraud, did not hesitate to administer ammonia to some

of his patients with cirrhosis of the liver in order to discover whether in this condition there is actually an impaired capacity to make urea from ammonium salts. It was reasoned that if the liver no longer produced urea because it could not do so, the ammonium salts would reappear in the urine as salts of ammonia. As a matter of fact this was not the case; the ammonia introduced reappeared in the urine, not as ammonia but as urea, while the total output of nitrogen of ammonia remained as before. You will realise that this test was very thoroughly carried out when I tell you that in one case as much as 9 grams of ammonia was taken. Only in the period of the death agony was there observed to be a distinct impairment in the capacity of the liver to form urea. I think the conclusion drawn from these experiments, namely, that the capacity of the cells for urea formation cannot be markedly impaired during life, is not very far from the truth.

We have also some interesting observations on urea formation in acute phosphorus poisoning in man. In a well-marked case of acute phosphorus poisoning the nitrogen of ammonia was reduced from 16·56 per cent. to 6·2 per cent. in consequence of the administration of sodium bicarbonate. This experiment indicates that the increased excretion of ammonia in this instance was dependent merely upon the presence of an excess of acid products in the organism. Had the ammonia been derived from the impaired synthesis power of the liver, the administration of a sodium salt for the purpose of supplying the place of ammonia in neutralising the acid would not have been followed by a diminution in the ammonia output.

We may now sum up by saying that the liver is a highly important seat of urea formation, that the urea excretion may be diminished in liver disease while the ammonia is correspondingly increased, and that this decrease in the elimination and formation of urea is apparently not due to failure in the synthetic abilities of the liver-cells, but to the diversion of ammonia for the purpose of neutralising acid products which threaten to reduce the alkalescence of the blood. It cannot, however, be denied that there exists the possibility that, in certain cases of hepatic disease which are nearing a fatal termination, the liver-cells lose their ability to make the amount of urea that should be made in health.

Having now examined the evidence in regard to the

urea-forming function of the liver in health and disease, we may take up the consideration of the liver in its relation to other aspects of proteid metabolism. It was at one time very generally supposed that the liver is largely concerned with the formation of uric acid. This view probably arose chiefly from the theory that uric acid is a precursor of urea in the nitrogenous metabolism of the organism. There is no substantial evidence that the liver is concerned in an important way in the formation of uric acid in the case of mammals. On the contrary, what evidence we have is distinctly opposed to this view. In the first place, there are numerous observations which show that in diseases of the liver, such as obstructive jaundice, cirrhosis of the liver, acute yellow atrophy, and acute phosphorus poisoning, the uric acid excretion either falls within normal limits or is moderately increased. It has also been observed in acute yellow atrophy that the administration of thymus gland was followed by an increased excretion of uric acid, as in health. We should hardly expect these results if the liver were the chief seat of the formation of uric acid. As I shall explain to you more fully in my next series of lectures, we now know that uric acid is derived largely from the physiological breaking down of the nuclei of cells—perhaps most largely from the leucocytes, but also from the cells of the organism generally. Anything, therefore, which actively stimulates destructive metabolism in the cells of the body at large is followed by an increase in the excretion of uric acid. This is doubtless the explanation of the increased formation of uric acid in some cases of acute yellow atrophy and acute phosphorus poisoning. A similar increase has been observed in dogs after the Eck fistula has been established, and after the experimental destruction of portions of the liver through the injection of acids into the bile-passages. The liver, therefore, cannot play more than a subsidiary *rôle* in the production of uric acid in dogs.

Although they possess no clinical importance, I am tempted to mention the observations on the excretion of uric acid in ducks and geese which were made by Minkowski after the removal of the liver from these animals. You know that in most birds the chief nitrogenous excretory product is uric acid, and not urea. Perhaps you also know that in birds a portion of the blood leaving the intestinal area passes by way of the renal vein into the general circulation.

This fact is important to the investigator because it makes it practicable to tie the portal vein at its entrance to the liver without producing rapid death. Advantage was taken of these anatomical conditions to throw the liver out of the general circulation by ligating both the portal vein and the hepatic artery. Interestingly enough, this elimination of liver functions was followed by an enormous diminution in the excretion of uric acid and by a proportionately large increase in nitrogen of ammonia. The ammonia thus excreted was united to lactic acid. These ingeniously conducted experiments furnish us with positive indications that in the case of geese and ducks the liver is the chief seat of the formation of uric acid. This is probably true for all birds.

There has been much discussion as to the meaning of leucin and tyrosin in the urine in the course of liver disease, and it is proper for us to briefly consider the subject here. You are aware that these amido-acids have been discovered in the urine, chiefly in cases where there is a rapid destruction of liver-cells—as, for instance, in acute yellow atrophy of the liver. More rarely leucin and tyrosin have been discovered in the urine of patients suffering from phosphorus poisoning. It has also been claimed that these bodies are sometimes found in the course of severe typhus and in small-pox, but it is not clear that this claim is well substantiated. It is certain, however, that the amido-acids are sometimes observed in obscure febrile disease, in which acute yellow atrophy or phosphorus poisoning is out of the question. Sometimes leucin and tyrosin exist in the urine in sufficient amount to separate spontaneously in the well-known crystalline forms; but, as a rule, it is necessary to resort to a special procedure in order to secure the crystallisation of these bodies from the urine.

It is believed that whenever leucin and tyrosin find their way to the urine, they exist also in the liver. It is certain that in many cases of destructive liver disease, such as acute yellow atrophy, the amido-acids are present in surprisingly large amounts. How are we to interpret the appearance of these bodies in the urine and in the liver? It has been asserted that their presence is to be explained on the supposition that they are no longer oxidised after the liver-cells have become markedly altered. That the amido-acids are altered through splitting and oxidation in the body is a well-known fact based on the observation that leucin and tyrosin

absorbed from the gut in considerable amounts cannot be detected in the urine. Leucin is undoubtedly completely burned in the body, an ammonium molecule being, perhaps, split off and utilised in the synthesis of urea. Similarly, in the case of tyrosin, an amido or ammonia group is split off from the molecule and utilised in the synthesis of urea. Tyrosin, however, differs from leucin, as you will remember, in the very important respect that it contains an aromatic nucleus. This aromatic nucleus is not broken up in the organism. It is probably eliminated as a phenol, in combination with sulphuric acid, in the form of an ethereal sulphate. Now, there is no good reason to believe that the spitting off of the amido-group from leucin and tyrosin is a function of the liver. At least, we can say that the experimental exclusion of the liver from the circulation has not been followed by the presence of leucin and tyrosin in the urine. Moreover, in geese from which the liver has been removed the nitrogen of the amido-acids reappears in the urine in the form of ammonia, which, of course, can only indicate that there are other parts of the body than the liver in which the separation of the amido-group from leucin and tyrosin may take place. We are, therefore, without sufficient reason for regarding the appearance of leucin and tyrosin in the urine as an indication that these bodies are not oxidised in the liver in consequence of the impaired oxidative functions of this organ. It appears much more probable that the amido-acids found in the liver and, to a smaller extent, in the urine in the course of acute yellow atrophy are dependent on the breaking down of the liver-cells themselves. There is, of course, no reason why the protoplasm of these cells should not be decomposed under pathological conditions with a yield of leucin and tyrosin, just as these bodies can be obtained from the breaking down of proteids in the course of digestion. That the large yield of leucin and tyrosin in the liver depends upon the presence of bacteria is far from being proved, but seems not improbable. That a certain amount of leucin and tyrosin should find its way into the urine in conditions where these bodies are so largely formed in the liver is not at all surprising. In many cases, however, leucin and tyrosin are formed in the liver in considerable amount, but do not find their way into the urine. Thus the absence of these bodies from the urine is no indication that great alterations in the liver are not taking place. The

large amount of leucin and tyrosin found in the liver in some cases of acute yellow atrophy appears in itself very much in favour of the origin of these bodies from the liver-cells themselves. The only other source of which we can think is the proteid contents of the intestine.

It is very generally thought that the appearance of the amido-acids in the urine is of grave prognostic significance. Probably this is in general true; but I know of instances of obscure febrile disease in which these bodies have appeared in the urine for several days in succession, and in which the patient has made a good recovery.

You will probably infer from what I have told you that the presence of leucin and tyrosin in the urine is only rarely helpful in diagnosis, and I think the inference is fully justified.

In many instances of liver disease, associated with extensive destruction of liver-cells, peptone-like bodies have been found in the urine. These substances are probably albumoses. They have been found not only in the urine, but also in the liver itself, in some instances in association with leucin and tyrosin. We know little of their significance, but are justified in suspecting that, like the amido-acids, they are products of decomposition of the liver-cells. While these substances have been found in the course of acute yellow atrophy and phosphorus poisoning, they are by no means constantly present in the urine, even in advanced and typical examples of these states.

Let us now consider some of the derangements in the glycogenic functions of the liver that occur in the course of disease. Unfortunately our knowledge of this subject is by no means proportioned to its importance, and I have little to tell you that bears in a direct way upon the better understanding and more intelligent treatment of hepatic disease.

You are of course aware that the liver-cells store the carbohydrate which we call glycogen for the uses of the organism, much as plants lay by their supply of starch. There is, indeed, a close resemblance between glycogen and starch, notwithstanding certain gross differences in physical properties, as, for instance, that glycogen swells up in cool water and passes into a state of partial solution. In percentage composition glycogen is the same as starch $(C_6H_{10}O_5)_n$, but its chemical structure is just as little known. Glycogen further resembles the early product of

starch digestion, known as erethro-dextrin in striking a red colour with iodine. Still another point of resemblance lies in the fact that both glycogen and starch yield dextrin on being decomposed.

In a previous lecture I mentioned to you the conversion of the carbohydrate food-stuffs into glycogen through the intermediate stage of glucose formation, and also the close relation between the liver content of glycogen and the absorption of carbohydrate food products from the alimentary tract. On a diet rich in carbohydrates the glycogen of the liver reaches from 12 to 15 per cent., while in a state of starvation it falls to a very low percentage, or may be so reduced as to escape detection. The quantity of glycogen falls so low during starvation because the organism is then compelled to draw on its carbohydrate reserve. When the diet contains an abundance of carbohydrate the capacity of the liver to store glycogen is soon exhausted, and the glucose which finds no room in the cells of this organ passes into other structures, and especially into the cells of the muscles, which, like those of the liver, convert glucose and store glycogen, but have a much smaller storage capacity, weight for weight. Where the storage capacity of the muscles as well as of the liver has been taxed to the utmost limits, sugar appears in the urine, and we have a state of alimentary glycosuria.

The accumulation of glycogen in the liver is subject to pathological as well as physiological variations. We know nothing of excessive glycogen storage, but are familiar with states in which the accumulation is distinctly diminished. Thus in many instances of diabetes the glycogen content of the liver is very low, and in phlorhizin diabetes the liver may be entirely freed of its carbohydrate. It was long ago noticed that after ligation of the common bile-duct puncture of the floor of the fourth ventricle no longer leads to glycosuria, and this observation was explained on the supposition that the glycogen of the liver had disappeared. More recently the interesting fact has been noted that ligation of individual branches of the hepatic duct is followed by disappearance of the glycogen from the jaundiced portions of the liver which correspond to these individual ligations. It is likely that in human obstructive jaundice there is a similar diminution in the hepatic glycogen.

What interpretation shall we place on this reduced

glycogen store in the liver? Are we to look upon it as indicating that the liver-cells fail to convert sugar into glycogen, or that they fail in the ability to lay by carbohydrate material? Although this question is one of fundamental interest, it is still involved in obscurity, and I shall not consume your time in reviewing the opinions that exist with regard to it. I cannot, however, pass without at least a reference to the influence of the nervous system upon the glycogenic functions of the liver. The physiologist Claude Bernard showed by his classical experiments that certain lesions of the central nervous system, especially puncture in the floor of the fourth ventricle, near the vaso-motor centre, are followed by glycosuria. His explanation of this remarkable phenomenon was that the nervous injury leads to an unduly rapid transformation into sugar of the glycogen laid up in the liver, and that this rapid transformation so considerably increases the percentage of sugar in the blood of the hepatic veins, and consequently in the blood generally, that a part of the sugar finds its way into the urine. That the glycosuria in puncture diabetes really arises from the liver glycogen is indicated by the fact that if this glycogen be removed through prolonged starvation injury to the central nervous system is no longer followed by the appearance of sugar in the urine. We have no satisfactory explanation of the way in which injury to the central nervous system brings about the derangements in liver function. It has been conjectured that the disturbance of hepatic function depends on deranged circulation in the liver following stimulation of the vaso-motor centre, and that defective oxygenation of the blood in the liver, due to stasis, may act on the liver-cells in such a way as to stimulate them to excessive metabolic activity. Whatever may be the real explanation of puncture diabetes, the fact that lesions of the central nervous system are sometimes causes of glycosuria is indisputable.

After what I have said of the diminution in glycogen that is found in the liver-cells after experimental obstruction to the common bile-duct, one would be justified in expecting that persons with jaundice should be less capable of storing glycogen in the liver than normal individuals, and one might further suppose that this disturbance in glycogenic function would show itself in a ready appearance of sugar in the urine after the ingestion of large amounts of carbohydrate

food. There are, indeed, investigators who claim that such an alimentary glycosuria is more readily brought about in patients with jaundice, with cirrhosis of the liver, and other forms of hepatic disease, than in persons who are in normal health. But the facts neither bear out our theoretical conceptions of what ought to take place if we transfer the results of animal experiments to human beings, nor do they bear out the clinical claims which I have just mentioned. A careful study of the question shows that glycosuria is only an occasional occurrence in patients with well-marked functional and structural derangements of the liver-cells. And we are justified in saying that patients with jaundice and with well-marked structural diseases of the liver, not merely digest and absorb carbohydrates like healthy individuals, but seem capable of storing them in the liver or elsewhere as in health. This is a fact of considerable practical importance to you as physicians, for it gives a clear therapeutic indication for the diet of patients with hepatic disease.

We come now to the examination of what is surely one of the most important and interesting functions of the liver —namely, its action as a detoxicating or antitoxic organ. It is by means of this detoxicating function of the liver that toxic substances entering the organ through the portal vein or the hepatic artery are converted into bodies which are less toxic or are wholly destroyed, by oxidations and decompositions, or are simply taken up by the liver-cells and temporarily stored. Although this detoxicating action of the liver has been the subject of numerous investigations during the past forty years, we have still very much to learn, not merely as regards the chemical nature of the processes involved, but also as to the real facts relating to the efficiency of the liver as an agent in destroying or modifying different sorts of poisons.

What I have to tell you about the liver as a protective agent against poison is based chiefly on two kinds of evidence: first, the evidence that various poisons suffer a diminution in activity during their passage through the liver; and second, the evidence that structural or functional damage to the hepatic cells leads to an accumulation in the body of toxic substances, which under normal conditions are rendered harmless through the agency of these cells.

The earliest observations on the antitoxic functions of the

liver relate to nicotine. It was found by Heger that nicotine added to the portal blood of an experimental circulation through the liver very soon disappears. Similar experiments with hyoscyamine, strychnine, morphine, and quinine showed that these vegetable alkaloids are in part retained in the liver. Later experiments gave confirmation to these results, and it is maintained that these alkaloids are not merely held by the liver-cells, but suffer a change in chemical composition, by which they lose their toxic character.

In the case of the metallic poisons we know that the liver acts as an important place of storage. Many metals and metalloids, including copper, lead, tin, mercury, manganese, antimony, iron, silver, zinc, and iodine, are held by the liver-cells, sometimes for long periods of time. It is not likely that these elements are retained as metals, but it is not clear in what combinations they exist. It may be that some of these substances are held in the cells in the form of oxides developed under the oxidative action of the hepatic cells, or it may be that the metals enter into a combination with the protoplasm of the cells. The deposit of these elements in the liver, when the portal of entry is the digestive tract, serves to screen other organs from the injurious effects of their presence. It is improbable, however, that this action of the liver is wholly a mechanical one, for it seems likely that the retention of the elements mentioned is associated, at least in some instances, with the formation of new compounds into which the cell protoplasm enters in some manner still unknown to us.

While it is, of course, very desirable that we should be informed in regard to the action of the liver upon poisons which, like those I have just mentioned, are often employed as therapeutic agents, it seems to me that a greater interest attaches to the fate of toxic substances that are formed within the organism as the result of digestive, metabolic, or bacterial activities. Even in health toxic materials are constantly being formed in the organism as the result of these activities, and it behoves us to inquire what disposition is made of them.

Of the substances formed in the digestive tract during digestion may be mentioned indol and phenol, aromatic bodies resulting mainly from bacterial action. I have already spoken to you of the origin of these bodies in connection with our study of putrefactive processes. I am able to tell

you some things about the relation of the liver to these bodies, because of experiments recently made in my laboratory. The object of these experiments was to determine whether the liver-cells possess any action in protecting the organism, and especially the central nervous system, from the injurious influence of these aromatic substances. In one set of observations the organs of healthy rabbits were quickly removed after bleeding nearly to the point of death. Definite quantities of the liver and other organs were chopped to a fine pulp, and then allowed to stand in the most intimate contact with measured solutions of phenol or indol of known strength. At the ends of various periods of time the mixture of organ pulp and solution was subjected to distillation, and the distillate employed to discover the quantity of phenol or indol recoverable from the original solution. It was found that the different organ pulps possess in different degrees the power of causing disappearance of the phenol or indol with which they are brought in relation. In the case of phenol the liver in every instance showed greater activity in disposing of this substance than the kidney, the muscle, the brain, or the blood. Only the epithelia of the intestinal tract gave results comparable with those obtained in the case of the liver. Similar results were obtained from the experiments with indol. It was further observed that it is possible to impair this activity of the liver-cells in some degree by subjecting the experimental animal to various pathological conditions. Especially noticeable was the reduced activity which was brought on by prolonged anæsthesia by chloroform or ether. But it was not found possible to bring about a great reduction in these cell activities by means of any form of damage inflicted during life.

A second series of experiments upon phenol and indol was carried out through the use of intravenous infusions of these substances in solution. Usually the injections were made until the animal showed definite nervous symptoms, such as fibrillary or clonic spasm, increased reflexes, and pupillary changes. The animals were killed promptly and definite weights of the liver, kidney, muscle, brain, and blood were subjected to distillation. By means of colour-tests carried on with the distillates it was possible to form an estimate of the quantity of phenol or indol existing in the different tissues at the time of death or very shortly after.

In the case of indol it was found in a very large proportion of cases that the liver yielded more colour than any other tissue. This striking result can hardly be accounted for except on the ground that the liver is more active than any other tissue in removing indol from the blood. There certainly is no reason to think the liver less active than any other tissue if we can be guided by the results of the contact experiments which I described to you a few minutes ago. The ability of the liver to dispose of the indol stored up in the liver-cells at the end of the infusion is illustrated by the fact that if the animal be permitted to live until the lapse of twenty or thirty minutes the quantity of indol which is present as such in the liver-cells is no greater than that found in other organs.

That the liver-cells take up phenol and indol from the blood in considerable quantity and hold them in a transformed state appears to be shown by these experiments and by others which I am unable to describe for you here. I think we are fully justified in saying that the liver exerts an important protective action in regard to these substances, which, as you will recall, are capable of irritating the central nervous system to over-action when present in excessive amounts in the blood. What is true of phenol and indol among aromatic derivatives of proteid putrefaction is very probably true of other more or less toxic aromatic bodies with which we are less well acquainted.

A detoxicating action on the part of the liver-cells has been shown to exist for another class of bacterial poisons, namely, the specific toxic proteids formed by pathogenic micro-organisms. Thus it was found that when extracts of typhoid bacilli were injected into the branches of the portal vein there appeared to be a distinct reduction in the toxic properties of these extracts. Again, experiments with the tetanus toxin indicate that the liver-cells are the most active of any in the body in neutralising this poison. Lastly, it has been observed that alcoholic extracts made from the bacillus pyocyaneus are distinctly less toxic when introduced in the portal system than when put into the general circulation.

I have now given you a sufficient number of examples of the detoxicating action of the liver to illustrate the variety of poisons that fall within its influence. It would not be difficult to multipy these examples were it desirable to do so.

It appears to me more important that I should try to answer a question which I am sure has already arisen in your minds: What is the nature of the activity by which the liver-cells exert their protective influence against poisons? By what chemical or physical processes do the hepatic cells act on poisons so different as the alkaloids, the heavy metals, the aromatic products of putrefaction, and the bacterial toxins? Although I am unable to answer this question fully, I can at least give you a notion of some of the processes involved in detoxications by the liver. Perhaps you recall what I told you about oxidation, synthesis, and methylation in our talk about the chemical defences of the organism against disease. If so you will better understand what I have to tell you now.

You will remember that I tried to explain to you the immense importance of the oxidative processes that go on in the organism at large in the tissue cells. Now the liver is probably the seat of the most intense oxidative processes that go on in the body, and these physiological processes of oxidation are turned to account in dealing with poisons. Thus the same processes of oxidation which enable the liver-cells to burn to carbonic acid and water the citric, malic, tartaric acids, &c., which they receive from the intestine in conditions of health enable them to oxidise and decompose alcohol, acetic acid, and many other organic substances of the fatty acid series which are capable of exerting distinctly poisonous activities when present in the intestine in considerable amount. In the case of which I have just been speaking the process of oxidation is associated with or followed by decompositions which may lead to the complete oxidation of the toxic bodies to carbonic acid and water. Oxidations frequently take place, however, which do not lead to decomposition. For example, the heavy metals like lead and arsenic probably undergo simple oxidation, and are then stored in the liver-cells, sometimes during very long periods of time. It is, of course, obvious that in cases of this sort any decomposition is out of the question. In the case of indol an oxidation takes place by which the indol is converted into the radical indoxyl. A decomposition involving the benzene nucleus which exists in aromatic compounds is unlikely, as I have already explained to you that the human organism is ordinarily incapable of disrupting the carbon atoms linked together in the benzene ring.

The oxidation of indol to the radical indoxyl is merely

one step in the process of protecting the organism against the toxic activities of this aromatic body. This stage of oxidation is immediately followed by a stage of synthesis in which the indoxyl radical combines with sulphuric acid given off from the cells with the formation of indoxyl potassium sulphate. Now, as I have already told you, this compound is distinctly less toxic than indol, from which the body thus protects itself. Synthetic processes of this kind, carried on by the liver-cells, are exceedingly important as agents in detoxication. Phenol or carbolic acid undergoes a synthesis with sulphuric acid like that which occurs in the case of indol, except that the antecedent process of oxidation is supposed to be left out in this case. I told you a few minutes ago that both indol and phenol disappear to some extent when their solutions are brought into contact with fresh liver-pulp. When I say these aromatic bodies disappear as the result of such contact I mean that we are no longer able to recover them in full amount if we practise distillation of the liver-pulps. If they were present in the form of indol or phenol, they would, of course, distil over. The fact that a certain quantity of these aromatic substances is held by the liver indicates that some transformation has taken place in the cells of this organ. The nature of this transformation is quite unknown to us. I suspect that it is in the nature of a temporary combination with the protoplasm of the liver-cells, and does not involve any marked transformation in these bodies. My reason for thinking this is chiefly the fact that if we inject phenol or indol into the organism we recover these bodies completely although in combination with sulphuric acid. If they suffered any marked chemical change during their sojourn in the liver-cells, we could hardly expect this to be the case. I am perhaps taking you into a little deeper water than is absolutely necessary when I enter into discussions of this kind. My excuse for doing so is that facts of the kind I am telling you certainly help us to understand a little more clearly the admirable processes by which the organism is capable of bringing about the detoxication of aromatic substances and possibly also of substances not belonging to this class. I do not suppose that I need to dwell on the significance of the liver-cells being capable of temporarily holding such bodies as phenol and indol from the general circulation during the time which is required to bring about a complete conjugation

with sulphuric or other acids. During this sojourn in the liver the nervous system is protected from injury. Another important synthetic activity of the liver-cells relates to the formation of urea from ammonia and carbonic acid, a function to which I have already made sufficient reference. Still another synthetic activity is that by which the methyl group, CH_3, enters into the composition of various bodies, as, for example, in the change from indol to methylindol or skatol, and the change from glycocoll to methyl glycocoll or sarcosin. To what extent these changes are antitoxic and to what extent they are carried on in the liver is at present uncertain. I refer to this subject of methylation merely because it is probably a further example of the varied functional activity of the liver-cells.

It has been thought that some of the alkaloidal bodies are merely held temporarily in the liver-cells without undergoing chemical transformation. You can see that even a temporary sojourn on the part of poisonous alkaloids in the liver-cells would be highly beneficial to the organism by the gain in time, which would, of course, enable the nervous system to better withstand any dangerous toxic effect. But I am inclined to think that, in many instances at least, an actual chemical transformation takes place which is destructive to the toxic properties of the alkaloids. There is experimental evidence that this is the case with hyoscyamin.

I have told you something in another connection about the supposed nature of the antitoxin formation which occurs in response to the stimulus of certain bacterial poisons. It is probable that the liver-cells play an important part in the manufacture of some antitoxic substances; but beyond what I have already told you as to the nature of the antitoxin formation I have nothing to say on this subject.

There is one point in connection with our discussion of the detoxicating activities of the liver to which I must especially direct your attention. It is that we are not justified in regarding these functional activities as being in any sense specific towards foreign poisons. The protective action is rather to be regarded as being merely the expression of physiological activities turned to account for an unusual purpose. Thus the processes of oxidation, of methylation, and of synthesis, which are so effectively employed in dealing with toxic substances foreign to the organism, are the same agencies that the organism employs constantly in

dealing with toxic bodies formed in health, as the result of digestive and metabolic activities. I wish also to remind you that where poisons are able to act upon the liver-cells in sufficient concentration the tax upon these cells often exceeds physiological limits and leads to structural damage in the cells. The precise character of the damage varies, to some extent, according to the nature of the poison. Most frequently it consists in fatty or albuminoid degeneration of the liver-cells.

While we have still very much to learn as to the chemical character of the processes involved in some of the detoxicating activities of the liver, we have, at least, the satisfaction of feeling certain that this organ is concerned in various ways with the revision of the composition of the blood flowing through the portal vein and through the hepatic artery. It would be an error to imagine that the liver is the only organ capable of carrying on important processes of detoxication, and I trust I have not given you this impression while speaking with such especial reference to this organ. It is, of course, possible that some of these protective activities are possessed by the liver exclusively, but there is no proof that this is so. There is no doubt that the cells of the muscles, of the kidneys, and of the spleen and the epithelial cells of the digestive tract are capable of carrying on many antitoxic functions of the same nature as those which I have described for the liver. But the liver, nevertheless, occupies a unique position among the structures adapted to protect the organism against the effects of poison. In the first place, its cells are more active than any others in the body in neutralising the effects of certain poisons, such as phenol and indol, and it is not unlikely that this superiority extends to other substances. Secondly, the liver is so large that the quantitative efficiency of the organ must be very great. Lastly, the liver occupies a remarkable position in being so placed that it receives the blood from the intestinal area containing many products of digestion unfit for the general circulation. Among these bodies are ammonia, phenol, indol, and, probably, albumoses and peptone. This position, as the sentry of the systemic circulation, is in itself suggestive of important functions in the revision of the composition of the blood, and, as I have already pointed out to you, this idea is certainly supported by experimental evidence.

I cannot leave the subject of the protective functions of the liver without at least a reference to the action of this organ upon bacteria. This action appears to be of two kinds. First, there is the destruction of micro-organisms by the inclusive and phagocytic action of the endothelial cells of the capillaries of the liver and of the leucocytes in the hepatic blood-vessels. Of course the phagocytosis by leucocytes is a property of the blood rather than of the liver, but I refer to it because it is thought to occur actively in the hepatic circulation. This retention of dead or injured micro-organisms within the liver has been noticed in the case of many pathogenic and non-pathogenic bacteria. Secondly, the liver acts through the agency of the bile as an eliminative channel for bacteria. There has been some discussion as to whether bacteria find their way from the blood-capillaries to the bile-capillaries without first injuring the intervening structures. That these structures may suffer in the course of the bacterial transit is certain; but it is likely that the elimination of some micro-organisms occurs physiologically and without inflicting appreciable damage. That the elimination occurs rapidly is shown by experiments in which the staphylococcus pyogenes aureus reappeared in the bile thirteen minutes after injection into a vein.

I now invite your attention to the consideration of the evidence that toxic substances accumulate in the blood and elsewhere when the functions of the liver are wholly or partially eliminated, either experimentally or through the agency of extensive disease of the liver-cells. I have already mentioned to you that when the portal blood is diverted from the liver after the establishment of an Eck fistula the animals soon die with the distinct indications of a toxæmia —that is to say, with marked prostration, convulsions, and coma. That these symptoms are due to the presence of an ammonium compound in the blood is in the highest degree probable. This is as much as we are justified in saying. We do not know in what form the ammonia exists in the blood under these conditions. Neither can we feel certain that other substances do not contribute to bring about the fatal toxæmia.

I regret to say that having told you of the toxæmia following the Eck fistula I have told you all that is at present positively known about intoxication due to failure in hepatic functions. In disease of the liver associated with advanced

and extensive damage to the liver-cells there is frequently an increased excretion of ammonia, but it is doubtful whether the slightly increased ammonia content of the blood is responsible for clinical manifestations.

Notwithstanding our very limited knowledge concerning the accumulation of toxic substances in the blood in complete or partial failure of hepatic functions, much has been written to prove that such toxæmias exist. The evidence in support of this view consists chiefly of the experimental results obtained by certain French writers who practised intravenous infusions of urine into rabbits and other animals. It is claimed by these writers that by means of their method of study it is possible to detect variations in the toxic properties of the urine which are significant of disease. Thus one writer reports an increase of urinary toxicity in numerous instances of catarrhal jaundice, chololithiasis, and atrophic and hypertrophic cirrhosis. Others find an increased toxicity of the urine in carcinoma and in tuberculosis of the liver. I could multiply examples of results obtained by this method of intravenous infusions of human urine in hepatic and other forms of disease, but should be wasting both your time and mine were I to do so. The truth is that this mode of experimentation as hitherto practised is so untrustworthy that it is outside the pale of scientific methods. I should like very much to enter on a full discussion of this question with you, but the time at our disposal does not permit me to do so. There are, however, certain facts in this connection which it is important for you to know. The human urine in health is quite highly toxic when infused into the circulation of rabbits. After the introduction of a quantity varying from 20 to 75 c.c. per kilo. of rabbit the animal develops dyspnœa, fibrillary twitchings, tonic and clonic convulsions, and soon dies. The death of the animal appears to be caused in a very large degree by the presence of the inorganic salts of the urine, especially the chloride of potassium and salts of ammonium. There are other toxic bodies in the normal human urine, but they probably play a comparatively insignificant part. Physical conditions have also to be taken into account in a consideration of the factors contributing to the toxicity of the urine. The degree of concentration of the urine is of the utmost importance. The volume of fluid is also a factor. Now in order to feel certain that a urine contains substances of an organic

nature, which render it distinctly more toxic or distinctly less toxic than normal, it would be necessary for us to know at least the exact composition of the urine as regards its mineral constituents. This, however, was never determined in the experiments of which I just spoke to you, and we cannot feel sure that the supposed variations from the normal have not been dependent on physiological variations in the content of inorganic salts. You can see how little scientific value such results as these must possess in the presence of such a possibility as this. Even if it could be shown definitely that the urine is more toxic than normal in certain diseases of the liver, owing to the presence of organic poisons, we should not be greatly enlightened, for we should still be wanting in our knowledge of the nature of the toxic bodies. It seems to me that we cannot speak positively of the presence of toxæmias in hepatic disease until we have succeeded in isolating the substances concerned in such toxæmias, and have familiarised ourselves with the nature of their physiological action.

Thus the facts which I have now brought to your notice indicate that while the liver plays an important *rôle* as a detoxicating agent there is no substantial evidence that well-defined toxæmic states arise from such defects in liver functions as are occasioned by chronic hepatic disease. It can at least be said that the cells of the liver are often extensively and markedly altered, as in atrophic cirrhosis, without the presence of any evidences of a well-defined toxæmia. This may be accounted for partly on the ground that the liver is normally capable of doing much more work of an antitoxic nature than is ordinarily imposed on it. Another important consideration is the fact that the cells of other organs are doubtless capable of compensating in a considerable degree for the falling off in the detoxicating processes of the liver. The muscles probably have a decided influence in effecting such compensations, and the kidneys aid by the rapid elimination of excretory elements of the blood which may be formed in excess. The increased work imposed upon the muscles, kidneys, and other structures under these conditions may perhaps be the cause of distinct impairment of health in the course of hepatic disease. We are, however, much in the dark as to this subject, and I have no established facts of importance to bring to your notice in this relation. It is possible that in time we shall find out

something as to the chemical nature of slight toxæmic conditions dependent on failure of the antitoxic liver functions.

Do not allow me to give you the impression that the diminished functional capacity of the liver in neutralising poisons is a matter of slight importance to the organism in the course of structural liver disease. Although we do not know how the effects are brought about, clinical observation shows us that many of the victims of chronic hepatic disease involving the liver-cells are liable to suffer from headache, depression of spirits, undue fatigue, nervousness, &c., whenever they commit slight indiscretions in diet. The rapidity with which such symptons disappear when the diet is suitably restricted in quantity and kind at least suggests that the improved clinical condition is connected with a more adequate transformation of toxic substances by the liver-cells.

You will not often be called upon to treat patients suffering from acute disease of the liver, which, like acute yellow atrophy and the acute degeneration of phosphorus poisoning, are accompanied by rapid cell destruction. Perhaps it is fortunate that this is the case, since we are almost helpless in the presence of conditions like these. The case is very different with the common chronic diseases of the liver associated with slow cell destruction. In a general practice you will meet with many cases of cirrhosis of the liver and of fatty degeneration of the liver, and you can do much by thoughtful treatment to benefit these patients. You know that many cases of cirrhosis of the liver appear to be dependent on the excessive use of alcohol. Probably the alcohol acts in part directly on the liver-cells, but it is almost certain that it acts also by setting up chronic gastritis. As a result of this chronic gastritis or gastro-enteritis toxic substances formed in the digestive tract reach the liver, and in the course of time occasion serious alterations in its cells. There is also good reason to think that chronic gastritis from any cause is capable of inducing degenerative alterations in the liver, perhaps with an overgrowth in connective tissue. Fatty livers arise under similar conditions. Alcohol is certainly an important cause of fatty changes in the liver, and this is true of both acute and chronic gastro-enteritis. In young children fatty livers are common sequels to severe gastro-enteritis. We do not know the precise conditions of the digestive derangement which lead to the fatty liver as

distinguished from the cirrhotic liver. Very often, as you are aware, the cirrhotic and fatty changes are combined.

You may ask, How are we to recognise the existence of cirrhotic or fatty degeneration of the liver? The diagnosis of cirrhosis is clear enough when the stage of obstructive portal circulation is reached, and we have ascites, splenic enlargement, &c. But cirrhotic changes occur long before this condition is reached, and the most advanced fatty livers give rise to no appreciable disturbance in the portal circulation. Sometimes a change in the size of the liver helps us in the diagnosis of atrophic cirrhosis, but frequently the percussion boundaries are quite normal. We are justified, I think, in suspecting the presence of a cirrhotic or fatty liver in every case of long-standing chronic gastritis, accompanied by persistent and marked loss of weight and strength, and by the ready production of headache, mental depression, &c., by food of such quality and quantity as occasions no disturbance in normal persons. Where gastric dilatation exists this syndrome is much less significant. A history of marked alcoholism or of syphilis under these circumstances favours the diagnosis of cirrhosis.

Some disturbances of digestion play so important a part in the production of chronic diseases of the liver that they demand the closest attention in any plan of treatment. Whatever favours the persistence of chronic gastro-enteritis indirectly favours the development of degenerative changes in the liver-cells. You must therefore conscientiously devote your attention to bringing about a subsidence in the gastro-enteric disturbance which almost regularly exists in persons with cirrhotic or fatty livers. I need not repeat what I have already said about the treatment of gastritis, but will speak of some points in connection with the diet of hepatic patients which seem worthy of mention. The glycogenic function of the liver appears to be little disturbed even in advanced cirrhosis. One would therefore expect that carbohydrate foods should be well tolerated. Clinical observations show that this is actually the case so long as we guard against the evils of excessive fermentation.

What are the theoretical indications in regard to the use of fat in disease of the liver-cells? The liver-cells in cirrhotic as well as in fatty livers contain a considerable excess of fat, and this excess is probably due to distinct impairment in the oxidative processes carried on by the

damaged cells, fat being more difficult to burn than any form of food. It would therefore seem wise not to burden the organism with the task of utilising a considerable amount of fat. We find in practice that it is best to allow our patients with chronic hepatic disease only a moderate quantity of fatty food. A certain amount of proteid is essential to replace cell-waste, and this our patients must have. In health people usually eat more proteid food than is required, and this excessive use of proteid must be avoided because it leads to unnecessary work in the production of urea, an activity carried on largely in the liver. Is there any choice in the character of the proteid food to be used by the subjects of chronic hepatic disease? It seems to me that the proteids of milk possess many advantages over those of meat On this subject I have already spoken at considerable length. In this connection, however, I may remind you that the small yield of putrefactive products from casein in intestinal digestion is one of the advantages of a milk diet in cases where we wish to spare the liver unnecessary work in the processes of detoxication. Another advantage of milk is the small yield of ammonium in the digestion of the milk proteids. On a meat diet the portal blood has been shown to contain a much higher percentage of ammonium than on a diet of milk. This alimentary ammonium has to be converted into urea, and this conversion, as I have already mentioned to you, appears to occur exclusively in the liver. The synthesis of ammonia of alimentary origin may impose a considerable burden on the liver if we permit the free use of meat. Very much of this work may be spared by using proteids in the form in which they occur in milk. You understand, of course, that the synthesis of urea, from the ammonia derived from cell metabolism throughout the body, is in no wise effected by the quantity of ammonia that reaches the liver from the alimentary tract. We can minimise this work of urea formation from the ammonia of cell metabolism by giving our patients an abundance of carbohydrate food, but a certain amount of urea production is essential to the maintenance of life. The point I am making in connection with the diet of chronic hepatic disease is that we should spare the liver unnecessary work in making urea from ammonia of alimentary origin. You accomplish this by giving proteid chiefly in the form of milk and by restricting

the use of meat proteid. Observation at the bedside indicates that patients with cirrhosis of the liver do better on milk proteids than on proteids of meat. Thus you see that a diet consisting very largely of carbohydrates and of milk is especially indicated in the class of patients we are discussing, and it is a satisfaction to note how close is the agreement between the theoretical and the practical indications for the selection of a dietary.

Many patients with cirrhosis of the liver show increasing impairment of nutrition after the onset of ascites. One is often compelled to resort to repeated tapping for the removal of the ascitic fluid. Fortunately surgical ingenuity has devised a method for the relief of the obstructed portal circulation which, though not fully tested, promises well, and has already caused the subsidence or disappearance of ascites in a number of instances of cirrhosis. The operation has for its object the establishment of other channels than the overcrowded portal system for the return of the blood from the intestine. There is every reason to think that if we can overcome the mechanical difficulties which find expression in ascites the lives of patients with cirrhosis of the liver may be indefinitely prolonged, since under good hygienic conditions the functions of the damaged hepatic cells are susceptible of extensive compensation.

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LECTURE XII

DIABETES

Diabetes as a pancreatic disease—Alimentary glycosuria—Doctrine of renal diabetes—Phlorhizin glycosuria—Difference in sugar-content of blood in phlorhizin glycosuria and human diabetes—Difficulties in estimating the sugar of the blood—Jecorin—Cause of hyperglycæmia—Evidence against over-production of sugar—Diminished combustion of sugar; hypotheses—Glycuronic acid—Effects of complete extirpation of pancreas—Evidence regarding existence of a glycolytic ferment—Relation of the pancreas to human diabetes—The 'islands of Langerhans'—Diabetes connected with defective storage of glycogen—Glycosuria after injuries to the head—Effects of loss of sugar in diabetes—Loss in weight and strength—Polyuria and thirst—Other symptoms connected with glycosuria—Lipæmia—Cataract—Effects of hyperglycæmia—Acid intoxication in diabetes—Excretion of β-oxybutyric acid—Influence of acid on the removal of alkali—Supply of ammonia—Excretion of ammonia—Excretion of other bases—Reduction in alkalescence of the blood—Diabetic coma—Its dependence on acid intoxication—Other effects of withdrawal of alkali—Origin and chemical relations of the organic acids—Summary—Hypotheses of intestinal origin of diabetes—Conditions influencing prognosis—Treatment.

I WISH to speak to-day of a highly important consequence of pancreatic disease—namely, the condition known as diabetes mellitus. Ten years ago the facts known to us hardly sufficed to justify one in classifying human diabetes as a pancreatic disease; to-day it is clear that in many instances of diabetes in man there is an intimate and peculiar relation between the appearance of sugar in the urine and the condition of the pancreatic gland. It is indeed possible that a derangement of pancreatic function is at least a factor in every case of true diabetes. The pancreatic function which stands in so close a relation to diabetes is apparently quite distinct from that which is concerned with the production of the pancreatic juice, and which we have already discussed in connection with intestinal digestion.

Diabetes is a disease of nutrition characterised by the persistent occurrence of glucose in the urine, even when the patient is on an ordinary mixed diet containing only a fair allowance of carbohydrates. The mere presence of sugar in the urine does not, of course, constitute diabetes; for, as you are probably aware, sugar may appear in the urine of normal persons when an excessive quantity of sugar or other carbohydrate material is taken with the food. To this appearance of sugar in the urine, owing to carbohydrate excesses in diet, the term 'alimentary glycosuria' is applied. It is important to distinguish carefully between this condition and true diabetes, but the distinction is not always easy to make.

It is not difficult in normal individuals to induce a glycosuria in which the urine contains as much as one or two per cent. of sugar, if one administers 100 grams or more of glucose, or saccharose, or lactose when the stomach is empty, as on rising. But if one obtains such a glycosuria from 100 grams of sugar later in the day, when digestion is active, the subject must be regarded with some suspicion, for we have to deal with the condition known as alimentary glycosuria *e saccharo*. Such a condition may be diabetic in character in the sense that it is the first indication of a true diabetes, but on the other hand the subject of alimentary glycosuria *e saccharo* may never develop diabetes. The observation that in really diabetic persons an amount of amylaceous food, corresponding to 100 grams of glucose, almost invariably gives rise to glycosuria, may help you to recognise a diabetic in a doubtful case.

The fact that the urine of some persons has a sweet taste has been known to European physicians for more than two hundred years, and there is reason to think that the Hindoos recognised diabetes much earlier, and referred to it as honey urine. But it is only a little more than a century since a physician of Liverpool, named Dobson, shewed that the sweet taste of diabetic urine depends on the presence of sugar.

Ever since the recognition of diabetes investigators have been unsparing in their efforts to determine the cause of so remarkable a phenomenon as the appearance of sugar in the urine. It was supposed at one time, and not unnaturally, that diabetes was referable to injury of the kidney, which permitted the escape of sugar from the blood into the urine,

in much the same way that lesions of the kidney allow the escape of albumin. There is indeed evidence that an experimental diabetes can be induced which owes its existence in part to a slight and peculiar form of damage to the structures of the kidney. This is the condition known as phlorhizin diabetes. Phlorhizin is a glucoside with the empirical formula ($C_{20}H_{24}O_{10}+H_2O$), which is obtained from the root-bark of the cherry, apple, pear, and plum. When administered to dogs by the mouth or hypodermically it quickly gives rise to the appearance of sugar in the urine. Zuntz found that the injection of phlorhizin into one renal artery is followed almost immediately by the presence of sugar in the urine excreted by the corresponding kidney, whereas a greater lapse of time occurs before the urine from the opposite kidney shows the presence of sugar. This indicates that phlorhizin injures the kidney directly in such a way as to permit the escape of sugar from the blood.

It must be confessed that we are still in the dark in reference to the nature of the glycosuria from phlorhizin. There is no doubt that the drug causes a marked reduction in the sugar content of the blood, although some investigators contend that there is an increase. Thus in one of my dogs the reducing substance of the blood was equal to 0·191 per cent. of glucose before the hypodermic administration of 1 gram of phlorhizin, which was followed in forty minutes by a second dose of the same size. One and a half hour after the last dose the reducing substance in the blood was only 0·133 per cent. It is conceivable that a mere injury to the kidney suffices to produce the glycosuria, but I suspect there is some factor in the production of this glycosuria with which we are at present unacquainted. One might imagine the sugar of the blood to be in some way protected against combustion at the same time that the permeability of the kidney is increased. But opposed to this idea is the fact that the sugar of the blood is not increased by phlorhizin even after the kidneys have been thrown out of the circulation. The sugar may indeed be diminished. Thus the renal vessels were ligated in a dog whose blood contained 0·225 per cent. of sugar. After the operation 2 grams of phlorhizin were given. After three and a half hours we found 0·199 per cent. of sugar, after twenty-six hours 0.119 per cent., and after fifty hours 0·155 per cent.

Although there seems little question that some peculiar

injury to the kidney is a prominent feature of phlorhizin diabetes, we do not yet understand the nature of the damage.

We have thus in phlorhizin diabetes a highly instructive example of glycosuria dependent on injury to the kidney, although in the slighter grades of the condition it is not possible with ordinary methods of investigation to detect structural renal alterations. Were it not for one well-established fact, we should perhaps be justified in looking upon phlorhizin diabetes as a strong argument in favour of a renal element in human diabetes. This fact is that whereas the blood in phlorhizin diabetes regularly contains a diminished quantity of sugar the blood in human diabetes usually, if not regularly, contains an increased quantity of sugar.

The importance of this difference in the sugar-content of the blood in the two forms of diabetes will be clear to you when I tell you that any increase in the percentage of sugar in the blood is followed by a prompt appearance of sugar in the urine. In a normal dog the sugar-content of the blood varies from 0·05 to 0·20 per cent. under ordinary conditions. If now we increase this percentage to 0·3 per cent. by intravenous infusion of a glucose solution, the urine contains sugar so long as this slightly elevated sugar-content of the blood is maintained. In other words the normal kidneys readily permit the escape of sugar when it is present in distinct excess in the blood; and this ready permeability of the kidneys is an entirely satisfactory explanation of the glycosuria connected with hyperglycæmia, or excess of sugar in the blood.

It was formerly contended with great confidence that the blood of diabetics always contains an excess of glucose. But a careful consideration of the evidence bearing on this important point leaves one with the feeling that we cannot yet generalise safely in reference to the relation between the sugar-content of the blood and the sugar-content of the urine. The subject is complicated by the fact that a part of the reducing-substance of the normal blood does not exist as sugar, but as a combination of glucose with lecithin—the so-called jecorin first described by Drechsel. There seems to be little doubt that the greater part of the reducing-substance of the normal blood exists as lecithin-sugar or some similar combination, and there are some writers who go so far as to claim that all the normal reducing-substance exists in this form. Now it happens that the different

methods used for the determination of sugar in the blood differ in that some give only the glucose-content, while some give the glucose and all the jecorin, and still others probably give the glucose and only part of the jecorin. These differences in methods are probably responsible for some of the discrepancies in the results of different observations on the reducing substances of the blood of diabetic patients.

Allow me, in passing, to call your attention to some figures from Henriques relative to the sugar of the blood in diabetes :—

—	Glucose	Jecorin-glucose	Total Sugar	Glucose in Urine
	%	%	%	%
I. Woman . .	0·027	0·221	0·248	1·8
II. Man . . .	0·072	0·424	0·496	6·63
III. Man (in coma) .	0·128	0·125	0·253	1·78

Other difficulties in the way of learning whether the sugar-content of the blood is always increased arise from the normal variations in the same person and in different individuals, and from the fact, already mentioned, that even a slight increase of the sugar of the blood is followed by its elimination in the urine. Thus, according to Seegen, glycosuria may occur when the amount of sugar in the blood is even less than 0·20 per cent., an amount no greater than that normally found in some persons, but possibly in excess of the normal for certain individuals.

In spite of the difficulties to which I have referred, one thing is clear—namely, that in a considerable number of diabetic patients the sugar-content of the blood is increased beyond what can possibly be regarded as normal. This increase has been noted especially in the bad cases of diabetes, cases which usually show a considerable percentage of sugar in the urine. The facts about phlorhizin glycosuria make it clear that a condition of hypoglycæmia is consistent with sugar in the urine, and such a possibility cannot be denied in the case of man, but it is still only a possibility.

From what I have now told you it is clear that the glycosuria of those diabetics who have an excess of sugar in the blood is sufficiently explained by the presence of this excess.

But why should the sugar-content of the blood be increased? This question can be answered only by assuming the correctness of one of two alternatives. Either there is an increased production of sugar within the organism, or else there is a diminshed power of utilisation. As regards the possibility of an increased production of sugar, it is easy to see that such an increase would have to depend on an increased formation of glucose from the carbohydrates, or the fats, or the proteids of the food or tissues. We know that the formation of sugar from carbohydrates is an entirely normal process which cannot be made responsible for a pathological production of sugar, although it is probable that there is too rapid a conversion of glycogen into sugar in some glycosurias of nervous origin. It might, perhaps, be thought that the supposed increase in sugar-formation is dependent on some pathological conversion of the fats. But it is at once seen that such a view is quite untenable (except possibly in the terminal stages of diabetes), for the reason that clinical experience shows us that diabetics are capable of taking large quantities of fat without any increase in the sugar of the urine. The only remaining source for an increased formation of sugar is proteid or other N-containing material. It is very easy, however, to perceive why such a source of sugar would not account for the phenomena of diabetes. Three hundred grams of proteid would furnish about two hundred grams of carbohydrate material; but, as you are probably aware, 200 grams of carbohydrate food in twenty-four hours would not cause the appearance of sugar in the urine of a normal person; yet there are cases in which the urine contains much sugar on such a diet. Three hundred grams of proteid represents the average daily quantity in the diet of a normal adult. This amount of proteid could be very greatly increased without affording a basis for such an increased production in sugar as would lead to glycosuria.

It is thus clear that diabetes is not the consequence of an increased production of sugar. The alternative is that the disease depends on a diminished combustion of sugar in the organism, and there is no doubt whatever that this is the correct explanation of the increased sugar-content of the blood. The power of burning sugar constitutes a function of the most fundamental character, and the sugar burned in the body is the source of a large yield of caloric energy.

Now this power of utilising sugar is never wholly lost, even in the most advanced forms of diabetes. In such cases the quantity of sugar in the urine is always less than the amount which corresponds to the quantity of carbohydrate material placed at the disposal of the organism.

At the present time we are unable to see beyond the fact that in diabetes an essential condition is the inability of the organism to utilise its sugar. It is possible that there are several distinct ways in which this failure to utilise sugar arises, and it is conceivable that different types of diabetes are dependent on such differences in the nature of the disturbance which interferes with sugar combustion. Although I am unable to discuss this subject to my satisfaction, it is instructive to consider the chief possibilities as to the reasons why sugar is not adequately burned in diabetes. Three different possibilities have been suggested. First, the defective oxidation of sugar by the body-cells; second, the defective splitting of the sugar molecule; and third, the defective storage of glycogen. These three possibilities by no means exclude one another, but it is convenient to consider them separately.

Up to the present time it has not been possible to demonstrate that in diabetes the general oxidative powers of the cells are actually diminished. It is known that in diabetes the products of proteid metabolism urea and uric acid are approximately normal, and that the fats are oxidised as in health to CO_2 and H_2O. Experiments show that lactates are oxidised, as in normal individuals, to carbonates, which make their appearance in the urine, and that benzol is oxidised to phenol. Moreover, in many cases of diabetes, lævulose, a lævo-rotary sugar, is utilised in the organism. On the other hand we know that in respiratory diseases in which there is cyanosis and in experimental asphyxia sugar does not appear in the urine, as we should expect it to do were diabetes dependent simply on diminished oxidation. Then, again, we know that in phosphorus poisoning the oxidative activities in the body are distinctly reduced, but notwithstanding this glycosuria does not occur.

But although it appears by use of these methods that the capacity of the cells for performing certain oxidations is not distinctly impaired, it is clear that for some reason the oxidation of sugar or its decomposition products is only imperfectly carried on. As we should expect where con-

siderable carbohydrate material escapes oxidation, the quantity of oxygen lost in respiration is lessened in diabetes, in comparison with the quantity of oxygen consumed in normal persons. I hope you have noted well the distinction implied in what I have just told you. The point which I wish to make clear is that although there is an actual diminution in oxidative processes connected with the burning of sugar there is no definite evidence that the cells of the body have lost, even in part, their capacity to effect the oxidations just now mentioned. But you will ask, Why does it happen that sugar is not oxidised if the cells have not lost their oxidative capacities? I believe the correct answer is that the cells do not burn sugar because they cannot get at it in the form in which it is normally burned. In other words, it seems probable that in diabetics the difficulty lies, not in the oxidising abilities of the cells, but rather in an impairment of the capacity of the cells of the body to prepare the sugar for oxidation. We do not positively know in what this preparatory step consists, but it is generally supposed to be a process by which the sugar molecule or its derivative, glycuronic acid, is split or decomposed into smaller and simpler molecules. We do not, however, know the nature of these decomposition products. It has been thought that lactic acid is an important one, but it is not at all clear that this is the case. According to a view of diabetes which is favoured by many modern students of the disease, the real difficulty lies in the decomposition of sugar into these simpler molecules. If the decomposition occurred according to the usual physiological habit, the cells would probably have no difficulty in carrying on the further decomposition and oxidation which leads to the ultimate conversion of the sugar molecule into CO_2 and H_2O. I just now spoke of glycuronic acid as being a derivative of sugar which is perhaps concerned with the process of sugar splitting into smaller and simpler molecules. Glycuronic acid is, you will recall, very closely related to glucose, as indicated in the following formulæ :—

$$\text{Glucose } \begin{matrix}\text{COH}\\(\text{CHOH})_4\\\text{CH}_2\text{OH}\end{matrix} \qquad \text{Glycuronic acid } \begin{matrix}\text{COH}\\(\text{CHOH})_4\\\text{COOH}\end{matrix}$$

which show the replacement of two H atoms by one atom of O in the group CH_2OH. This process of oxidation is apparently brought about very readily in the normal organism, and

involves no disturbance of the linkage of the carbon atoms in the sugar molecule; the further oxidation of the glycuronic acid molecule into the final products of combustion, CO_2 and H_2O, is certainly a much more difficult task for the cells of the organism, because it involves the disruption of the linkage of the carbon atoms. It is perhaps just at this point where the separation of the carbon atoms occurs that the ferment of the internal secretion of the pancreas is effective. But, as we shall see presently, neither this ferment nor the internal secretion itself has been actually proved to exist. There is experimental evidence that the oxidation of glucose to glycuronic acid occurs even in the severest cases of diabetes. Thus Weintraud found in a very advanced patient (who was excreting organic acids in large amount) that glycuronic acid was still produced in considerable quantity. This glycuronic acid was excreted by the urine in consequence of the administration of chloral, camphor, and α-naphthol in the form of urochloralic acid, camphoglycuronic acid, and naphthoglycuronic acid respectively. The urine of diabetics may contain glycuronic acid compounds even when the patient is receiving no medication whatever. It may also contain pentoses or sugars containing five carbon atoms in the molecule-bodies closely related to glycuronic acid.

It is important for you to familiarise yourselves with the chemical properties of glycuronic acid and its compounds, not only because of the great theoretical interest which attaches to this first oxidation-product of glucose, but on account of its practical importance. This consists in the fact that it is by no means uncommon for it to appear in the urine after the medicinal use of morphine, camphor, naphthol, terpentinol, menthol, phenol, &c., when it is apt to be mistaken for glucose owing to its reduction of copper salts. I cannot here describe the methods of distinguishing between the glycuronates and glucose, but shall refer to the fact that while glycuronic acid, like glucose, rotates the plane of polarisation to the right, its compounds rotate to the left. Moreover the glycuronates do not ferment with yeast.

But, to return to the line of our argument, what evidence have we that impairment of the ability to decompose glucose or glycuronic acid is in reality the explanation of the lessened combustion of sugar? I confess that the foundation for this view is inferential rather than direct, and yet

it seems to me that it is necessary for us to assume this defective splitting of the sugar molecule or the glycuronic acid molecule in order to harmonise facts which I have told you about glycosuria and defective oxidation. Although we must regard it as probable that in health the process of sugar-splitting or of glycuronic-acid splitting is something distinct from the process of oxidation itself, we are in the dark as to how this normal cleavage is brought about. It is only natural that under these circumstances we should welcome any facts that appear to give us a clue to the correct explanation. The remarkable relationship between extirpation of the pancreas and diabetes furnishes us with such a clue.

You probably know that in 1890 Von Mering and Minkowski made the highly important observation that complete extirpation of the pancreas is invariably followed by the typical symptoms of diabetes—namely, glycosuria, rapid loss of weight and strength, great thirst, and a voracious appetite. These results were obtained in more than fifty dogs. In from twenty-four to forty-eight hours the glycosuria was at its height, and the urine was observed to contain from 5 to 11 per cent. of sugar. Even after a seven days' fast the glycosuria continued. On a diet of bread and meat the quantity of sugar lost in twenty-four hours amounted to from 70 to 80 grams in a dog weighing 8 kilos.

I have just mentioned to you that diabetes is produced when the pancreas has been completely removed. I must refer to this fact again in order to emphasise the important circumstance that the presence of even a small portion of the pancreas, say one-fifth or even less, usually suffices to prevent the occurrence of glycosuria. In one of my dogs there was no glycosuria, although I left less than one-tenth of the pancreas. We now know that there is a similar relationship between the pancreas and diabetes in the human subject. Disease of the pancreas often leads to diabetes, but the presence of a small portion of the gland may suffice to prevent the appearance of sugar.

What is the explanation of this experimental diabetes following the removal of the pancreas, and how does it aid us in the understanding of human diabetes? Perhaps the first idea that occurred to critics was that the removal of the pancreas leads to impaired digestion from the absence of the pancreatic juice, and that this is in some way responsible

for the occurrence of the glycosuria. But it is clear that this cannot be the correct explanation, since we have learned that ligation of the pancreatic duct does not cause diabetes, and that glycosuria may not arise unless almost the entire gland is extirpated. The criticism has been made that the diabetes following pancreatic extirpation is not dependent on the removal of the gland, but on the almost unavoidable injury to the solar plexus incidental to so severe an operation on an organ connected with this plexus. This objection to the pancreatic origin of diabetes cannot be sustained, for Minkowski succeeded in transplanting the pancreas under the skin at a distance from the normal position of the gland, with the result of preventing glycosuria, although it is evident that the damage to the nervous system is just as great as where simple extirpation was practised.

Having excluded the pancreatic secretion and the nervous connections of the pancreas as significant in the production of diabetes, there apparently remain only two possibilities. One of these is that the cells of the pancreas normally destroy or modify toxic substances produced in other parts of the body, and that after extirpation of the pancreas these substances are no longer destroyed, but accumulate in the blood and interfere with the combustion of sugar. All one can say in reference to this possibility is that there are no well-established facts to speak in its favour. If, however, it interests you to become acquainted with the arguments that have been advanced in favour of this idea, I advise you to read a recent paper by Tuckett, of Trinity College, Cambridge, in which he considers auto-intoxication the cause of pancreatic diabetes. The contention is made here that the pancreas has an internal secretion which enters the circulation constantly by way of the thoracic lymph, and that a toxic substance capable of causing glycosuria, if not neutralised by this internal secretion, is absorbed from the intestine during digestion, also by way of the lymph-stream. There appears to be some support for this view in the observation that if the thoracic lymph from a fasting dog is injected into the portal circulation of a cat no hyperglycæmia or glycosuria results ; but that if lymph from a digesting dog is injected into the portal circulation, thus giving the hypothetical poison a chance to act, there is produced a hyperglycæmia varying from 0·3 per cent. to 0·9 per cent., and a glycosuria varying from 1 per cent. to 9 per cent.

These observations require to be repeatedly confirmed before we attach much weight to them.

The alternative is that the pancreas normally makes an internal secretion which is necessary to the splitting and utilisation of the sugar molecule. Such an internal secretion may be imagined to exert a direct ferment-like action in splitting sugar when appropriated by the cells of the body which are concerned with the combustion of sugar, or, what seems less reasonable, may be *supposed* to act in an indirect way through an influence on the nutrition of the nervous system. The first of these views—namely, that there is an internal secretion which initiates glycolysis, or sugar-splitting—has been warmly advocated by the French investigator Lépine. Lépine called attention to an old experiment of Claude Bernard's, indicating that the sugar of the blood gradually disappears when the blood is allowed to stand. He also thought that his own experiments showed the blood of diabetic patients to have a diminished capacity to transform sugar—a contention recently revived by Biernacki. The impaired action of the blood of diabetics Lépine attributed to diminished production of a glycolytic ferment which it is a function of the pancreas to make.

At first sight this simple and ingenious hypothesis strikes one favourably. The experimental facts on which it rests unfortunately have not stood the test of close examination. It is true that several writers have claimed to find a diminished glycolytic action on the part of the blood of diabetics, but the studies of several careful workers have failed to substantiate this claim. Indeed, Lépine himself has given up the idea that the glycolysis occurs in the blood, and refers it to the cells constituting the sugar-burning tissues. This change in view is demanded by what we now know about the cells as the seat of oxidative processes. The action of the pancreas, according to the modified view of Lépine, is a secondary one, and consists in stimulating a glycolytic action of the cells through its trypsin ferment.

Experiments were recently made by F. Blumenthal which appeared to give strong support to the hypothesis that various kinds of cells—cells from the pancreas, from the liver, from the spleen, &c.—possess a powerful glycolytic or sugar-splitting action. These cells were subjected to great pressure in the hope of expressing any ferment they might contain, in much the same way that Buchner under-

took to express the ferment from the yeast plant. The addition of sugar to the juices prepared in this manner was followed by fermentation and by the disappearance of considerable sugar in the course of twelve or sixteen hours. Then the conclusion was published that the various cells possess a distinct glycolytic ferment. Fortunately these experiments were repeated before they could exert much influence on our views of the glycolytic action of the cells. It was found by Umber that when careful precautions are taken against contamination through micro-organisms, the tissues outside the body exhibit only a very slight glycolytic action. We have made some experiments in our laboratory relative to the supposed glycolytic action of the normal blood. Following the procedure of Biernacki, 1 gram of blood was added to 25 c.c. of a 1·6 per cent. solution of glucose and allowed to stand twenty-four hours at the room temperature. The mixture showed no loss of glucose in those cases where precautions were taken to prevent contamination. In the cases where the sugar was reduced in quantity the 'glycolytic' action was plainly referable to the presence of micro-organisms.

It has not been shown that the cells of the pancreas when removed from the body have any greater glycolytic action than those of other organs. Nor has it been possible to show that blood collected from the pancreatic veins has any greater activity in splitting sugar than has the general arterial or venous blood.

Without taking you further into the intricacies of this subject, I may sum up as regards the sugar-splitting activity of the tissues as follows. The cells of the body normally split and burn sugar. This is a fact beyond question. The process of sugar-splitting is perhaps carried on through the agency of a special glycolytic ferment, but we have no positive knowledge as to the nature of this ferment or its origin. We do not know whether it is a special and specific ferment, or whether it is a ferment which has other functions than that of splitting the sugar molecule. The fact that removal of the pancreas is followed by diabetes suggests that the ferment is furnished by the cells of the pancreas in the form of an internal secretion. But it is also conceivable that the action of an internal pancreatic secretion may be an indirect one, operating through its influence on the central nervous system. I do not consider that we are justified in discarding

the theory that diabetes depends on the failure of an internal secretion from the pancreas merely because we are unable to show that the pancreatic cells outside the body do not exhibit a distinct or considerable glycolytic action. There are some functions of cells which are well carried on outside the body, but there are others, like the synthesis of urea, which apparently go on only in the living cells under normal conditions. It is conceivable that pancreatic and other cells exert a glycolytic action under physiological conditions, but not after removal of the cells from the body. Yet, after all that can be said in favour of the existence of an internal pancreatic secretion, we cannot say whether the action of the secretion is that of a glycolytic ferment or that of an antitoxic secretion, which neutralises poisons capable of interfering with the combustion of sugar.

Careful histological studies of the human pancreas in health and in diabetes make it appear that the influence which this gland normally exerts on the combustion of sugar depends mainly or exclusively on the presence of clusters of irregularly polygonal cells, with spherical nuclei and homogenous refractive cell bodies. These clusters of cells, differing so markedly from the pancreatic cells of the ordinary glandular type, lie within the acini, are in peculiarly intimate relation with the vascular system, and are most numerous in the splenic end of the pancreas. They are usually known as 'islands of Langerhans.'

Since it is difficult to subject these structures to experimental injuries which do not, at the same time, damage the ordinary glandular cells, physiological methods have not thrown much light on the relation of these cell-clusters to carbohydrate metabolism. Ssobolow, indeed, states that after feeding animals on carbohydrates the cells of the islands become more granular. Moreover, he finds that after the ligation of Wirsung's duct in dogs the islands of Langerhans are not involved in the sclerotic changes which succeed this operation, and it is suggested that this is the reason why glycosuria does not occur under these conditions. But our chief reliance must be placed on the histological conditions observed in the human subject. First, there is the fact, noted by Opie in Welch's laboratory, that the islands of Langerhans show a resistance to the inflammatory process following obstruction of the human pancreatic duct; a condition in which, as you are aware,

glycosuria is not a feature. Next there is the fact, which we may regard as established, that in the interlobular variety of chronic pancreatitis the inflammatory process implicates mainly the periphery of the pancreatic lobules, and damages the Langerhans clusters only in an advanced stage of sclerosis. This fact harmonises well with the observation that diabetes is frequently absent in cases of well-defined chronic pancreatitis, although it is usually present in the extreme grades of the disease. Lastly, there is the very important circumstance that in the interaciner type of chronic pancreatitis, where the inflammatory process is diffuse and separates individual acini with the implication of the islands of Langerhans, diabetes appears to be regularly present. I say appears to be regularly present because a more sweeping statement is not yet warranted by the number of observations on the form of pancreatitis in which the islands are extensively involved. If we should find a single case of pancreatitis in which these islands are obliterated, but in which glycosuria is wanting, it would go hard with the hypothesis which correlates these peculiar structures with the function of burning sugar

Diabetic cases of the sort recently described by Opie, in which the islands of Langerhans have been destroyed or isolated from their vascular supply, while a considerable part of the secreting parenchyma is not markedly altered, are peculiarly significant in connection with the hypothesis of which we have been speaking, which seems in a fair way to be put on an impregnable foundation. And it must be evident to you that the establishment of a definite relationship between disease of the Langerhans clusters and diabetes would give material support to the doctrine of an internal pancreatic secretion, since these structures stand in such intimate relation with a rich vascular supply.

But even the most enthusiastic friends of the pancreatic origin of diabetes cannot yet claim that all cases of diabetes arise from pancreatic disease, for it appears extremely probable that some cases of diabetes are related to a defective storage of glycogen in the liver and muscles perhaps unconnected with disturbance of pancreatic function.

That the nervous system has a regulating action on the glycogenic function of the liver is a well-established fact. I have already mentioned that Claude Bernard induced glycosuria in dogs by making a puncture in the floor of the fourth

ventricle, between the nuclei of origin of the eighth and tenth nerves. A characteristic feature of such a glycosuria is that it lasts just as long as there is glycogen in the liver and no longer. If the animal be deprived of food after the puncture has been practised, the glycosuria soon stops, and the liver—perhaps also the muscles—is found to be nearly free from glycogen. If now the animal be fed on carbohydrate food, the puncture again becomes operative and glycosuria reappears.

What takes place after the puncture of the medulla is probably an abnormally rapid conversion of glycogen into sugar. How this is brought about we do not know. You can easily see that if the liver, instead of storing its glycogen as in health, should quickly convert it into sugar, the function of the liver as a carbohydrate storehouse would be greatly impaired. It seems probable that if the disturbance in carbohydrate storage were confined to the liver the muscles would be able to compensate very largely for the defective action of the hepatic cells. Probably this is what happens in diseases of the liver involving extensive destruction of its cells. Under these circumstances, as I have already explained to you, glycosuria does not occur much more readily than in health. In the case of the puncture diabetes the conditions appear to be different. It seems likely that the muscle-cells as well as the liver-cells are unable to store glycogen as in health. Whatever may be the mechanism involved in the hurried removal of glycogen from the liver-cells, it is clear that this process is followed by an excessive accumulation of sugar in the blood, and therefore by its appearance in the urine.

The glycosuria or diabetes associated with various forms of nervous disease may perhaps be regarded as arising in a manner similar to puncture diabetes. You have probably been taught that it is not very uncommon for injuries to the head to be associated for a time with glycosuria. In many of these instances the glycosuria appears very quickly after the infliction of the trauma. There is thus a resemblance between such cases as these and cases of experimental glycosuria following the Bernard puncture. In both conditions the sugar appears promptly after the injury, and in both cases the glycosuria is transitory. It is reasonable to think that the glycosuria is in both instances due to the irritation of nervous centres in the medulla oblongata.

There are, however, other examples of traumatism to the nervous system in which the clinical relations are different. There are some cases in which an injury to the head is followed after a time by the appearance of sugar in the urine. The sugar is persistent, and the case must be regarded as one of diabetes. It is not altogether clear how we should interpret such instances as these, but it seems probable that they are to be regarded as dependent on an interference with the glycogenic function of the liver, brought about by over-stimulation of nerve-centres. We may imagine that, as in the case of puncture diabetes, the carbohydrates coming into the liver are promptly swept out into the circulation in the form of sugar. There is, however, this important difference: in the case of the persistent diabetes there is probably a permanent organic lesion of the nervous system, and not a temporary physiological disturbance, as in the case of the puncture and some traumatisms to the head. A similar explanation is probably applicable to some cases of cerebral tumour, cerebral abscess, &c., accompanied with persistent glycosuria.

Thus you see it is probable that in the human subject diabetes may arise in at least two different ways: first, through impairment in the functions of the pancreas; and second, through injury of the nervous system, interfering with the glycogenic functions of the liver, and perhaps also of the muscles. The clinical facts speak in favour of the existence of these two types of diabetes. Still it is possible that the two sets of conditions are not so far removed in their pathology as one might at first suppose. It is conceivable that the derangement of the nervous system exerts some unknown influence on the pancreas as well as on the liver. We have still a good deal to learn as regards this possibility. I consider it very important for us to have careful histological studies of the pancreas in cases of diabetes supposed to be of nervous origin.

I have said enough for the present about hypotheses as to the origin of diabetes, and we may advantageously consider the disease from a different point of view, namely, the relation between the loss of sugar sustained by the organism and the symptoms of diabetes. Whatever may be the cause of the impaired consumption of sugar, it is clear that many of the leading symptoms of the disease can be referred to the loss of sugar which the organism suffers. As I have

told you on several occasions, the carbohydrates are in health an important source of caloric energy to the body—in fact, the most important source. If on an ordinary diet a patient becomes unable to utilise a portion of his carbohydrate food, the organism loses an amount of potential for the production of heat and power exactly proportionate to the quantity of sugar found in the urine. Every gram of glucose that finds its way into the urine represents a loss of four and a half gross calories, or nearly four net calories. Now a loss of 100 grams of sugar in twenty-four hours would occasion a loss of nutritive potential equivalent to about 400 calories. A patient passing daily 2,000 c.c. of urine containing 5 per cent. of glucose would lose this amount of nutritive potential, and diabetic cases of this grade are not very rare. So considerable a regular loss of energy—equivalent to nearly one-sixth of the total caloric expenditure—sooner or later becomes inconsistent with the maintenance of a good state of nutrition. So long as the patient digests and absorbs enough food to supply fully or nearly the caloric needs of the body, in spite of the persistent loss of glucose, the weight, and even the muscular power, is well maintained. But the time arrives when this is no longer possible : the quantity of food-material absorbed is no longer sufficient to maintain the caloric expenditures in the face of the glycosuria. Then there is the loss in weight and power so characteristic of advanced diabetes. I suspect that the liability to muscular fatigue is not wholly due to the diminished size of the muscles, but depends partly on the deprivation of sugar which the muscle suffers. (Lecture II.)

Two other important symptoms of diabetes—polyuria and excessive thirst—are referable to the considerable loss of glucose through the kidneys. If we experimentally increase the sugar-content of the blood in a dog or other animal, there is a prompt increase in the volume of the urine. Some increase in the volume of the urine always attends the excretion of a considerable quantity of sugar, doubtless because the additional supply of fluid is required to enable the epithelial cells of the kidneys to perform the work of separating glucose from the blood. The amount of urine passed by some diabetics amounts to 4,000 or 5,000 c.c. in twenty-four hours, but in cases where the quantity of sugar in the urine is less than 1 per cent. the volume of the urine may not be appreciably increased.

When the body loses more water by the urine than it would lose in a urine containing only the normal ingredients, the cells of the body suffer a reduction in their content of water, since the volume of the blood is maintained by withdrawal of water from the cells. The need for more water in some obscure way affects the nervous system and calls forth the sensation of increased thirst observed in so many diabetics. Chronic gastritis may be another cause of excessive thirst in a diabetic.

There are several other important but indirect pathological consequences of the glycosuria of diabetes. Some of these depend on the readiness with which the sugar of the urine undergoes fermentative decomposition. In consequence of such decomposition it is not uncommon for pruritus or slight dermatitis to develop in the parts about the urinary outlet; and this liability emphasises the necessity for strict personal cleanliness. In exceptional instances the urine in the bladder has undergone fermentative changes.

In advanced cases of diabetes the blood contains a larger amount of fat than normal, and the liver is the seat of a well-marked fatty infiltration. The percentage of fat in the blood may increase to a point where the presence of fat is recognisable by the naked eye, and the patient is said to have a lipæmia. This increase of fat in the blood is closely connected with the occurrence of a marked glycosuria. The smaller the amount of sugar the organism is able to burn the larger becomes the demand on the fats and the proteids, and a greatly increased combustion of fat means the presence of an unusually large amount of fat in the blood. If for any reason fat is deposited in the liver faster than it is burned by the cells of this organ, a fatty infiltration arises. These phenomena attendant on the increased metabolism of fat can be experimentally induced in dogs by the use of phlorhizin.

The relation between the loss of sugar in diabetes and the development of cataract has not been clearly established. This condition is apt to appear in marked cases of diabetes, and is perhaps the expression of the impaired nutrition of the crystalline lens. That it does not depend on the presence of an excess of sugar in the blood is clearly indicated by the fact that cataract can be experimentally induced in dogs by means of phlorhizin, which diminishes the sugar-content of the blood.

Whether any of the symptoms or signs of diabetes besides glycosuria can be referred to the excess of sugar in the blood is, I think, still a question. It has been suspected that the general pruritus and the neuralgias are in some way dependent on the hyperglycæmia, but there is no satisfactory evidence of this. It has also been suggested that the marked susceptibility of diabetics to various infections, including infections from pyogenic organisms, is due to the excess of sugar in the blood. We have no proof of the correctness of this contention, and it must be confessed that there is at least a likelihood that this susceptibility is in some way connected with the impaired nutrition of the cells which results from the loss of sugar and from the accumulation of deleterious substances such as organic acids. It is also conceivable that some alteration in the ferment-like 'complement' is the cause of the diminished bactericidal power of the blood. (See Chapter I.)

The peculiar behaviour of diabetic blood towards various colouring agents has also been attributed to a hyperglycæmia, but without good reason. You may have had your attention called to some of the reactions that were first described by Dr. Bremer, of St. Louis. If so you will recall that a thick-spread film of normal blood, which has been heated to 135° C. and stained with a 1-per-cent. aqueous solution of Congo red, looks yellow to the naked eye, whereas a film made from the blood of a diabetic looks greenish brown. Similarly if one stains with methylene-blue a difference can be detected in the behaviour of normal and diabetic blood-films. Although these peculiar reactions can usually be obtained from diabetic blood, this is not always the case, and it is also true that they have been noted in pathological conditions, such as leukæmia and Graves's disease, unattended by an increase in the sugar of the blood. The absence of a dependence of these reactions on a hyperglycæmia is shown by the fact that we failed in our laboratory to obtain them either from the blood of dogs from which the pancreas had been extirpated or from blood in which the sugar-content was experimentally elevated by the intravenous infusion of a solution of glucose. On the other hand it seems clear that the blood reaction with methylene-blue, known as Williamson's reaction, depends on the presence of sugar.

But in spite of the paucity of our knowledge of the pathological effects of a hyperglycæmia I think we are justified

in believing that the presence of a large excess of sugar cannot be a matter of indifference to the organism. The sugar of the blood in diabetes may rise to 0·8 per cent., and we know that the experimental infusion of glucose solution in dogs may be followed by a marked excitability of the nervous system when the sugar-content of the blood exceeds 1 per cent. It remains for future studies to determine the pathological consequences of human hyperglycæmia.

It is no doubt natural that a large share of attention should have been given to a sign so readily detected as the presence of sugar in the urine. There is, however, another feature of true diabetes which is rarely, if ever, wanting in established cases of the disease, and which I consider of equal importance with the glycosuria. Indeed, I may say that in some instances it is of much greater practical significance. This highly important feature is a state of acid intoxication.

You will perhaps remember that in speaking of the chemical defences of the organism against disease I mentioned certain arrangements by which the organism is capable of effecting a neutralisation of pathological acids by means of alkalis, and especially ammonia, furnished by the body itself. (Lecture I.) The alkali, uniting with the pathological acid, forms a neutral salt, which passes through the kidneys, and thus relieves the individual of at least a portion of the acid. The larger the quantity of the pathological acid to be eliminated, the larger is the call made upon the alkali resources of the body, and the greater is the danger of exhausting these resources.

Now I wish to clearly impress upon you the fact that in every severe case of diabetes—that is to say in every case of diabetes in which the patient loses weight and strength from the failure to burn sugar—there is found in the urine a considerable quantity of organic acid. In the normal individual this acid is either not formed at all or is formed in relatively small amount; and, being oxidised in the body, does not find its way into the urine. In diabetes the organic body known as β-oxy-butyric acid is probably the chief pathological acid, and, being unburned in the organism, finds its way into the urine after entering into combination with alkalis as already mentioned. The quantity of this acid excreted in the urine is large in all severe cases of diabetes, often reaching 15 to 20 grams in the day, and under some conditions amounting to 60 grams. In mild

or early cases the acid may amount to only a few grams in the twenty-four hours, or may be altogether absent.

The presence of an acid in pathological quantities in the blood and tissues has an effect on the organism which is of first importance to vital processes carried on in the cells. This is the removal of alkali from the body. If we introduce an acid into the body either by way of the digestive tube or by direct infusion of a weak solution into the blood, this acid acts at once on the alkali present in the plasma and in the cells which it nourishes. The alkali of the blood exists chiefly as sodium carbonate and sodium phosphate, and it has been estimated that the amount of this 'alkaline reacting alkali' (or 'native alkali') in the entire body is equivalent to 60 grams of sodium hydroxide (NaOH). This amount of alkali is so small that it would be quickly exhausted by a persistent acid intoxication with a persistent formation of only small amounts of acid. Now we know that certain diabetic patients live months and years in spite of the fact that large amounts of acid are passed daily by the urine in combination with basic material, it being, of course, understood that the urine does not contain free acid. Since the 'native alkali' of the body is not sufficient to neutralise so much acid, it is apparent that there must be another and more permanent source of alkali than the native alkali. We know that this is actually so, and that the base is ammonia.

The supply of ammonia which is available for the neutralisation of acids is derived from two distinct sources. One of these is, as I explained in my first lecture, the proteid metabolism of the cells of the body generally. The other is the decomposition of proteid food, especially meat. In a state of health the ammonia derived from both these sources is in very large part utilised in the formation of urea. In a state of acid intoxication part of this ammonia is diverted from its usual destiny, and, instead of contributing to the production of urea, is utilised in the neutralisation of the pathological acid. In other words the pathological acid enters the urine as an ammonium salt. The native alkali of the blood, chiefly sodium and potassium, is thus spared—at least to a considerable extent.

The quantity of ammonia which is carried out of the body in a state of intoxication by acid may be very large. In a state of health less than 5 per cent. of the total nitrogen excreted by the urine exists as ammonia; in

diabetes the nitrogen of ammonia may exceed 20 per cent. of the total nitrogen. In exceptional instances the amount of ammonia may equal 8 or 10 grams in twenty-four hours. You can form some idea of the neutralising power of this ammonia when I tell you that 7 grams of the base will neutralise nearly 50 grams of β-oxy-butyric acid.

But although the human organism is thus capable of furnishing ammonia for the neutralisation of pathological acids there is a limit to this alkali resource. When the quantity of acid is so large as to exhaust the available ammonia the other bases are called upon—the sodium and potassium of the blood plasma, and even the calcium and magnesium of the bones. Thus it happens that while in some instances of diabetes we find that ammonia is the only base in the urine which has suffered an appreciable increase, in other cases we find an increase of ammonia, of sodium, of potassium, of calcium, and of magnesium. From what has just been said it is evident that the amount of ammonia gives us a clue to the quantity of pathological acid in the urine. This is, however, only a *rough* index of the degree of the intoxication. A much more accurate idea is obtained by the somewhat laborious process of determining the bases —ammonium, potassium, sodium, calcium, and magnesium —and comparing their total alkali value (expressed in terms of sodium) with the total acid value of the chief known acids of the urine—hydrochloric, sulphuric, phosphoric, and uric. In health the acids just about balance the bases, but in diabetic coma or in any state of acid intoxication the bases are in great excess of the *known* acids just mentioned. The amount of their basic excess corresponds to the quantity of some unknown organic acid or acids. Thus the following values were obtained in the day's urine of a healthy adult :—

Bases.	Gm.	*Acids.*	Gm.
K_2O	·9232	SO_3 preformed	·9733
Na_2O	3·881	SO_3 combined	·0356
CaO	·2154	P_2O_5 (bibasic)	·7432
MgO	·0806	P_2O_5 (monobasic)	·1987
$N(NH_3)$	·4707	Uric acid	·0584
		Cl	4·476
Total bases	5·5709	Total acids	6·4852

Here the total acids were in excess of the total bases by

·9143 gram. This apparent excess is not due to the presence of free acid in the urine, but to some organic base with which the acid is united.

Contrast these normal results with the results of balancing the acids and bases in the urine of a patient with advanced diabetes and threatening nervous symptoms. In such a urine the following values were obtained :—

Bases.	Gm.	*Acids.*	Gm.
K_2O	2·5540	SO_3 preformed	·6857
Na_2O	2·4450	SO_3 combined	·1253
CaO	·8035	P_2O_5 (bibasic)	·8521
MgO	·1973	P_2O_5 (monobasic)	·1756
$N(NH_3)$	3·1130	Uric acid	·0271
		Cl	1·5110
Total bases	9·1128	Total acids	3·3768

Here there is an excess of bases over acids equal to 5·7360 grams of sodium. This large amount of basic material is of course not present in the urine as free alkali, but in combination with an acid which is *not* one of the four acids considered in the analysis. As all the mineral acid was determined in the analysis, the acid in question must be an organic acid. Assuming that the acid is all β-oxy-butyric, the quantity of this body which would be neutralised by 5·744 grams of sodium is about 26 grams. Thus by balancing the acids and bases we can obtain evidence of the excretion of a large amount of organic acid.

Although the nature of the acid excreted in diabetes has been made the subject of numerous studies, the subject is one that calls for still further investigation. In 1884 Minkowski and Külz independently discovered in diabetic urine an acid which, on being subjected to ultimate analysis, yielded results corresponding to oxy-butyric acid. Other observers regard the chief acid of diabetic urine as amido-butyric acid. The evidence, however, appears to me distinctly in favour of the view that the chief acid is nearly always β-oxy-butyric acid—

$$\begin{array}{l} CH_2\text{—}COOH \\ | \\ CH.OH \\ | \\ CH_2 \end{array}$$

In some instances of diabetes, especially those in which the state of coma has been reached or is impending, diacetic acid $\begin{pmatrix} CH_2.COOH \\ | \\ CH_3.COOH \end{pmatrix}$ has been found in the urine. Indeed, some writers have attributed to this acid a principal part in the causation of coma. Recent investigations ascribe to it only a secondary *rôle*, for we know that it is frequently absent when oxy-butyric acid is present, and that, even in states of coma, diacetic acid rarely exceeds in amount 10 per cent. of the total organic acid of the urine.

Of other organic acids in diabetes we know at present almost nothing, but have to admit that other acids may possibly play a part in the development of states of intoxication.

I have explained to you that the acid which passes from the blood into the urine of diabetic persons withdraws alkali from the organism, sometimes in large amount. This fact gives us the key to an explanation of the symptoms that arise where there is a high grade of acid intoxication.

So long as the cells are able to offer sufficient ammonia for the neutralisation of the pathological organic acids that are found in the body the alkalescence of the blood is not diminished. But just as soon as this alkali resource proves insufficient for the complete neutralisation of the acid or acids, and sometimes sooner, the alkali of the blood is sacrificed to effect the necessary neutralisation. This results in a reduction in the alkalescence of the blood—a reduction which has been more than once demonstrable in diabetic coma, even by means of our present imperfect methods of determining the alkalinity of the blood.

A considerable permanent reduction in the alkalescence of the blood is incompatible with the maintenance of life in mammals. The reason for this is evident when we consider, even superficially, the conditions of the gas exchange in respiration. Thus we know that in the dog the venous blood contains from 39 to 48 percentage volumes of carbon dioxide, the arterial blood somewhat less. This considerable volume of carbon dioxide is held in the blood, not in a state of simple solution, but largely in combination with sodium. When an organic or mineral acid enters the blood it displaces the diffusible carbon dioxide and appropriates sodium, which leaves the blood by the kidneys as a sodium salt of

the pathological acid. It is easy to understand that if the amount of sodium in the blood is distinctly reduced, the carbon dioxide liberated in the cells can no longer make its way to the lungs to find an exit from the body. Thus it happens that there may occur an accumulation of carbon dioxide in the fluids and cells of the body sufficient to reduce the oxidations in the body to a point where it is no longer possible to maintain consciousness, or even to carry on the circulation. Coma and death are the extreme clinical expressions of this pathological condition.

It is well known to clinicians that persons with diabetes are peculiarly liable to die in a state of coma. In some instances this coma is clearly due to the ordinary causes of coma-cerebral lesions, uræmic intoxication, &c. But in a considerable proportion of cases the coma has certain well-defined clinical characters which distinguish it from other kinds of coma. The most important of these characters is persistent dyspnœa with rapid and deep respirations.

I think I can explain to you why it is that the typical coma of diabetes—the 'coma dyspnœicum diabeticum' of Kussmaul—is usually unassociated with cyanosis.

If we introduce into the circulation of a dog or rabbit a certain quantity of an organic or mineral acid, it is possible to bring on a state of dyspnœa sometimes associated with a stuporous condition. If now we determine the content of the arterial blood in carbon dioxide and in oxygen, we obtain characteristic and remarkable results. The carbon dioxide in the blood is greatly reduced in amount while the oxygen content remains normal. Thus in the classical experiments of Walter the percentage volume of carbon dioxide was easily reduced from a normal of 23–28 per cent. to 16 per cent., 8 per cent., or even less, while the percentage volume of oxygen remained very near the normal of 10 per cent.

The dyspnœa observed in animals poisoned by acid doubtless depends on the accumulation of carbon dioxide in the cells. The interference with necessary oxidation is due to this accumulation of carbon dioxide in the cells, and not to any diminution of oxygen in the blood. The blood contains enough oxygen, but the cells cannot get at it. It is important for you to understand that the coma observed in the course of an intoxication by acid is not a specific effect of β-oxy-butyric acid, but apparently depends merely

on the capacity of the acid to rob the blood of alkali, a property possessed by many other acids.

I know of only one observation on the carbon dioxide of the blood in diabetic coma. This was made by Minkowski on the arterial blood of a patient who had just passed into diabetic coma. The analysis showed only 3·34 per cent. of carbon dioxide, a reduction comparable only to that seen in the most extreme cases of experimental intoxication. It is important to note the fact that the urine of twenty hours contained 46·2 grams of oxy-butyric acid.

Several months before this observation a patient with glycosuria was brought into Naunyn's clinic in Königsberg in a state of coma. Blood taken from the radial artery was subjected to analysis in the belief that the case was one of diabetic coma. It contained 28·2 per cent. of carbon dioxide, a normal amount. The autopsy showed the existence of purulent meningitis, which was doubtless the cause of the coma. Although the urine contained 3·2 per cent. of sugar, no oxy-butyric acid could be found.

There is a disposition on the part of some writers to question the dependence of diabetic coma on an acid intoxication and to refer the condition to unknown toxins. While it is conceivable that unknown poisons may contribute to the development of coma, I look upon the causal relationship of acid intoxication to coma as an established fact. The evidence on which I lay the most stress consists, first, in the regular development of coma or stupor, whenever the excretion of acid is very large; secondly, the absence of typical diabetic coma when there is little or no excretion of acid; and thirdly, the remarkable improvement in the psychical state that follows the restoration of the alkalescence of the blood by the direct infusion of an abundance of alkali.

But coma is by no means the only consequence of the acid intoxication of diabetes. Long before the coma develops the diabetic patient commonly manifests a variety of nervous symptoms, such as headache, impaired mental activity, excessive drowsiness, and an alteration in disposition. Although the relation of these symptoms to the state of acid intoxication has not yet received the careful study which it deserves, I have satisfied myself that a relationship has existed in certain cases, the symptoms waxing or waning with the increase or decrease of the

excretion of acid. An important fact in this connection is that patients suffering from these cerebral symptoms of acid intoxication are peculiarly sensitive to the evil effects of constipation. The lapse of two or three days without a movement of the bowels may greatly exaggerate existing cerebral symptoms, while free purgation is followed by prompt and sometimes remarkable relief.

One of the effects of the persistent formation of large amounts of acid is the withdrawal of calcium and magnesium from the body. This loss is borne chiefly by the bones. The bases which enter the blood from the food being appropriated by the acid, the renewal of the slow physiological bone-waste becomes impossible, and the skeleton is thus weakened.

I think enough has been said to show you how important is this element of acid intoxication in the pathology of diabetes, though it must be owned that we cannot now measure its full significance. It must also be apparent to you that the influence of this element upon the prospects of our diabetic patients is one of the first importance. Indeed, I have no hesitation in saying that I believe the quantity of acid in the urine is a more reliable guide to the future of a diabetic than the percentage or quantity of sugar he is excreting. A patient with 2 per cent. of sugar in his urine may have an advanced acid intoxication, while a patient with 5 per cent. of sugar may be passing little pathological acid by the urine. A patient with only a few grams daily of oxy-butyric acid in his urine is certainly in no immediate danger of coma or of severe cerebral symptoms, whereas one who is passing 30 or 40 grams of this acid every day is on the edge of the diabetic precipice, if he has not actually passed into the terminal coma. Although there are exceptions to the rule, a large total loss of sugar in the urine is commonly accompanied by the presence of considerable organic acid.

It has doubtless occurred to you to ask how and where the pathological organic acids of diabetes are produced, and in what way their presence in the urine is related to inability of the organism to burn its sugar. These fundamental questions cannot be satisfactorily answered at present. There are, however, some facts relative to this subject with which it is important for you to be acquainted.

There is excellent reason to believe that both oxy-butyric

and diacetic acid, together with the body known as acetone, may originate from the metabolic decomposition of proteid substances. These three substances, which are very frequently associated in the same urine, are so closely related chemically that there is nothing improbable in the view that they have essentially the same origin in the body. Please consider for a moment this relationship. β-oxy-butyric acid—which we can represent as follows, $CH_3—CH(OH)—CH_2—COOH$)—can readily be oxidised outside the body into aceto-acetic or diacetic acid ($CH_3—CO—CH_2—COOH$) and there is no reason to doubt that a similar oxidation occurs within the human body, although I know of no experimental proof of such a transformation.

The relation of diacetic acid to acetone is a simple one. In fact diacetic acid, $CH_3—CO—CH_2—COOH$, very readily breaks up into acetone, $CH_3—CO—CH_3$ and into carbon dioxide, CO_2. This, doubtless, happens in the body as well as in the laboratory. The close chemical relationship between oxy-butyric acid, diacetic acid, and acetone explains why it is that these three bodies are liable to be found in excess at the same time in the urine of diabetics. Nevertheless the relation between these bodies is not necessarily such as to lead to their undergoing concomitant variations. We may find oxy-butyric acid in fresh urine without any diacetic acid, and we often find acetone in excess when neither diacetic acid nor oxy-butyric acid is to be detected.

Since oxy-butyric acid is the chief organic acid in the diabetic intoxication, and we have a fuller knowledge of it than of any other organic acid connected with this pathological state, I shall confine myself to a discussion of the origin and significance of this particular acid.

Oxy-butyric acid is generally believed by physiologists to be derived from the excessive metabolic decomposition of proteid, and there seems to be little doubt that at least a part of the acid which is found in the severest cases of diabetes has this origin. In most cases, though not in all, the organism is not in nitrogenous equilibrium, but is losing nitrogen at the time when considerable acid is being excreted. It does not follow that whenever the body loses nitrogen from increased metabolism of proteid we can find oxy-butyric acid in the urine. Proteid metabolism may be

increased in the early period of starvation, in poisoning by ricin, and after the administration of phlorhizin, but oxy-butyric acid cannot be detected in the urine. We find it, however, in the late stage of inanition, and soon after the extirpation of the pancreas, in both of which conditions there is increased proteid metabolism.

The presence of glycosuria is not a necessary condition for the appearance of oxy-butyric acid in the urine, for it has been detected in scarlet fever and in measles, in scurvy and in starvation. On the other hand the urine may contain large amounts of sugar, as in human diabetes and in experimental phlorhizin glycosuria, without the presence of organic acids in the urine. Yet it is to be noted that very large amounts of the acid have been found only in diabetes.

There is evidently some peculiar condition of proteid metabolism, entirely unknown at present, which is necessary for the production of oxy-butyric acid.

Within a few years investigations have been made to determine whether oxy-butyric acid may not under some circumstances arise from the imperfect combustion of fat. The recent studies of Magnus-Levy indicate that in diabetic coma the quantity of oxy-butyric acid formed and excreted is sometimes enormous. Thus in one instance the quantity of this acid and its derivatives amounted to 342 grams in three days, and it was calculated that of this quantity only 271 grams could have been derived from the combustion of proteids, the carbon contained in the destroyed proteid being far from sufficient to supply the carbon contained in the acid excreted. As the patient was receiving no carbohydrate food, the remaining 71 grams of oxy-butyric acid is attributed to fat, which, as you are aware, is burned in large amounts when the organism is deprived of carbohydrates. One source of error has, however, to be kept in mind when we interpret results like those noted by Magnus-Levy. This is that the amount of organic acid excreted by the urine in a given period is not necessarily all formed in that period or in a period of the same length. It is not impossible that, owing to some delay in the process of renal excretion, the amount of acid excreted in three days was actually formed during a longer period, say during four days. If this criticism be a legitimate one, it makes insignificant the evidence in favour of the origin of the organic acids from

fat. And it must be owned that such an origin is not in accordance with the results following the administration of fat in the diet.

If oxy-butyric acid were derived to a considerable extent from the imperfect combustion of fat, we should expect the acid to increase in amount when we substitute fats for carbohydrates, as we so often do in the treatment of diabetic patients. But we know from clinical experience that the condition of the patient greatly improves when we make the substitution of fat for carbohydrates, and this improvement is hardly consistent with an increase in the formation and excretion of oxy-butyric acid. Indeed, in one of my patients, a middle-aged woman with severe diabetes, the oxy-butyric acid in the urine fell gradually from 12·1 grams in twenty-four hours to 0·97 gram after the replacement of carbohydrates by fat. Subsequently she was permitted the use of carbohydrates, and oxy-butyric acid reappeared in considerable amount. I have noted similar results in other cases of diabetes.

It is therefore safe to say that we require much more evidence than has yet been offered to prove that a portion of the oxy-butyric acid of diabetes is derived from the imperfect combustion of fat. Having several times made the observation that the withdrawal of carbohydrates was followed by a reduction in the amount of oxy-butyric acid in the urine, I think we ought to look carefully into the possibility that part of the acid is derived from carbohydrates either from the food or from the carbohydrate radicle of the proteid molecule in the protoplasm of the cells of the body.

Before quitting the theoretical side of the subject of acid intoxication in diabetes I ought perhaps to mention some recent observations on the relation of butyric acid to acetone. Seelmuyden found when he administered butyric acid to dogs under the influence of phlorhizin the acetone excretion was increased. Still more recently Strauss and Philippsohn observed an increase of acetone from 56·9 milligrams in the urine of forty-eight hours to 200·2 milligrams when 20 grams of sodium butyrate were added to a constant diet. These results are suggestive because of the close relationship between butyric acid and oxy-butyric acid.

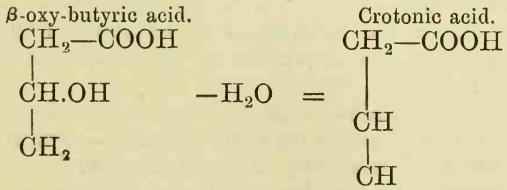
I hope I have now said enough about the acid intoxication

of diabetes to make you realise its practical significance. If you neglect to determine whether a patient under treatment has organic acids in the urine in pathological amounts, you are ignoring one of the most important guides in prognosis. Whenever a patient regularly passes more than 5 grams of oxy-butyric acid daily, the element of intoxication must be kept constantly in mind. The decline or disappearance of the acid under restriction of the carbohydrates of the diet is a favourable omen. On the other hand the gradual increase of the acid, in spite of careful dietetic regulations, carries with it an evil prognosis. But a patient may live for many months in spite of the fact that his urine contains daily an amount of acid equivalent to 15 or 20 grams of oxy-butyric acid.

Since the determination of oxy-butyric acid involves considerable labour, it is well for you to know that the amount of NH_3 excreted gives us a rough index to the excretion of the acid. Thus it is estimated that a daily output of 2 grams of NH_3 corresponds to about 6 grams, 5 grams of NH_3 to about 20 grams, and 8 grams of NH_3 to about 36–40 grams of the organic acid. The determination of the NH_3 is a comparatively simple matter.

Although the determination of the ammonia in the urine is a very useful guide to the excretion of organic acids, experience has taught me that the urine sometimes contains considerable oxy-butyric acid when the quantity of NH_3 falls within normal limits. For this reason I prefer another method for clinical work.

If the urine of a diabetic be concentrated and distilled with strong sulphuric acid, the oxy-butyric acid is decomposed into crotonic acid and water and the crotonic acid can be readily recovered from the distillate. The quantity of crotonic acid thus obtained gives a good idea of the amount of oxy-butyric acid present in the urine. The decomposition which takes place is indicated as follows :—



Owing to the removal of one molecule of H_2O from one molecule of β-oxy-butyric acid, the latter collapses into crotonic acid.

Passing in review the more prominent facts relating to the nature of diabetes, we see that the chief characteristic of the disease in its early stage is the inability of the cells of the organism to utilise carbohydrates. In mild cases the amount of unburned sugar is small, but in more severe cases the failure of the sugar-burning function is so considerable that the organism not merely fails to burn the carbohydrates of the food, but is unable to burn completely the carbohydrate moiety of the proteids of the body itself. In all such severe cases the inability to utilise sugar is accompanied by the production of considerable quantities of organic acids, chiefly oxy-butyric and diacetic, which are excreted by the urine in combination with ammonia and other bases. The loss of weight and strength, the thirst, and the polyuria which we observe in severe cases of diabetes, depend on the loss of sugar; many of the cerebral symptoms, including a peculiar type of coma, are due to the withdrawal of alkali through the agency of the organic acids. The fatal issue commonly depends on the union of these two distinct features.

The failure to burn sugar is closely related, in human diabetes, to disease of the pancreas. The nature of this relation is not yet clear, but we are justified in regarding it as probable in the highest degree that the cells of this gland normally make an internal secretion in some way necessary to the cleavage and oxidation of the sugar molecule. It is by no means proven that the pancreas is the seat of disease in all cases of human diabetes, and there are instances in which the glycosuria can be referred with much likelihood to disturbances in the central nervous system, which derange the glycogenic function of the liver. Whether the pancreas plays any part in the cases of true human diabetes which we suppose to be of nervous origin is at present uncertain, but it has not been shown that its influence can be positively excluded. As to the conditions of metabolism which lead to the formation and excretion of oxy-butyric acid we are still in the dark.

Some recent students of diabetes have advocated the view that the glycosuria has an intestinal origin, and is closely connected with the absorption of toxic substances normally formed in the digestive tract. These substances

find their way into the lymph, and are ultimately neutralised, in respect to their toxic properties, by meeting the hypothetical internal secretion of the pancreas. According to this view, which I have already mentioned, the unknown toxic substance may act as a poison on the cells of the body when it fails to be perfectly neutralised, either on account of the diminished formation of the pancreatic secretion or because the poison is produced in unusually large amount. The failure to burn sugar is ascribed to the action of the poison on the sugar-burning functions of the cells.

I mention this view of the nature of diabetes, notwithstanding it is but feebly supported by experimental evidence. The possibility that poisons originating from fermentative and putrefactive decompositions may in some manner impair the capacity of the cells to utilise sugar is certainly worthy of consideration. The character of these processes in diabetics has never been carefully studied. Efforts have, however, been made to induce diabetes in dogs by feeding them on fæcal material from diabetic patients. It is claimed by Töpfer that he succeeded in obtaining positive results from this procedure. Other observers have, however, entirely failed. It is also stated that the intravenous injection and the feeding of bacteria from diabetic stools yielded positive results in dogs and cats. The data are so few with reference to this important question that we cannot form a judgment of any value. I may mention, however, that I introduced considerable amounts of the fæces from a patient in diabetic coma into the intestine of a dog and into the stomach of a monkey without any appearance of glycosuria.

An attempt has very recently been made by Leo to prove that there must be some unknown toxic substance in the blood to account for the phenomena of diabetes. He argues that acetone, diacetic acid, and oxy-butyric acid do not occasion glycosuria, and that diabetic coma, the Bremer reaction, and the occurrence of neuritis cannot be explained by any known toxic agents pertaining to diabetics. On injecting subcutaneously into dogs the urine of diabetics, this writer finds that a glycosuria arises which cannot be accounted for by the sugar present in the injected urine. Hence the conclusion that the urine contains an unknown poison, derived from the blood of the diabetic and capable of setting up glycosuria. We have not time to discuss this hypothesis and the experiments on which it is based. I may

say, however, that I regard experiments of the sort on which this hypothesis rests as untrustworthy for scientific research and incapable of deciding the question at issue. I mention the experiments because it is proper for you to know that there are other hypotheses as to the nature of diabetes than the one I have presented to you.

In the few minutes that remain to us before the close of the hour allow me to call your attention to some points connected with the prognosis and treatment of diabetes. I have already intimated that the severity of a case of diabetes cannot be ascertained merely by determining the percentage and quantity of sugar in the urine. It is, indeed, not very uncommon to hear it said that a particular diabetic is not a bad case because his urine is not much increased in volume and shows only 1 or 2 per cent. of sugar. But if a patient on a diet much restricted in carbohydrates passes 1 or 2 per cent. of sugar in his urine, he may in reality be the victim of a severe form of disease, and may be in more danger than another patient who has 4 per cent. of sugar while eating a liberal amount of carbohydrates. Thus you perceive it is necessary to take into consideration the character of the diet before one forms a judgment as to the significance of the percentage of sugar in the urine. If you find that on greatly reducing the carbohydrates or on wholly withdrawing them from the dietary the urine no longer contains sugar, it is evident that there is still a considerable assimilative capacity for sugar on the part of the cells of the organism, because the body continues to burn completely the sugar which we know to be constantly split off from the proteid molecule in the course of the normal metabolism of the cell-proteids. On the other hand, the appearance of sugar after the withdrawal of carbohydrates shows that the sugar-splitting functions of the cells are so greatly impaired that the sugar derived from cell-proteid cannot be utilised. If sugar continues to appear in the urine after the complete withdrawal of carbohydrate for five days, the prognosis is unfavourable, and the larger the amount of sugar, in proportion to the nitrogen excreted, the worse is the outlook.

By experimenting with the carbohydrates of the diet we can determine for each diabetic patient the degree of his assimilative capacity for this class of food-stuffs. It is important to determine this, because a persistently low assimilative capacity is of evil omen, whereas a high or

increasing ability to use carbohydrates without producing glycosuria is a favourable prognostic indication. It is, however, to be borne in mind that the ability to assimilate carbohydrates is not a fixed thing in any patient, and that this ability may rapidly improve or rapidly decline.

Quite as significant as the assimilative capacity for sugar is the quantity of organic acid in the urine. An amount of acid in the urine, equivalent to one or two grams of oxybutyric acid daily, can be detected in many cases of diabetes which are running a mild and chronic course. Such quantities are consistent with a prolonged maintenance of life. But when the amount rises to 20 or 30 grams of acid in twenty-four hours, the normal alkalescence of the blood is threatened, and your patient is moving towards the brink of terminal coma. You can form some estimate of the imminence of this fatal event by watching the organic acids of the urine.

It is well known to clinicians that age influences the prognosis of diabetes in a very definite manner, the outlook being worst in the case of children and best when the disease begins in the second half of life. We can picture to ourselves why this should be so. In childhood the oxidative activities of the cells must be intense in order to carry on cell-growth in addition to maintaining the body. A disorder of the cells, which is so profound that the organism suffers in its assimilation of sugar, likewise impairs the capacity of the cells to grow. The oxidative activities essential to growth cannot be carried on, and development is at first retarded, and ultimately ceases. The patient now becomes susceptible to many intercurrent diseases, and is apt to die from one of these, if not from the coma of acid intoxication. In adult life the development of diabetes is probably less serious, because no provision has to be made for the further growth of the cells of the body, and the loss of sugar can better be sustained. In persons beyond sixty the cell activities gradually grow less intense than in adult life, and there is normally some loss in bodily weight. The loss of a little sugar by the urine is, under these circumstances, less important to the organism than when the full caloric expenditures of adult life have to be met.

The diabetes which follows traumatisms, or psychical insults, is less apt to progress rapidly than the cases of apparently spontaneous origin. Persons inclined to obesity

usually have a less serious type of diabetes than those who are poorly nourished. This, perhaps, has to do with the fact that in corpulent persons the capacity of the digestive tract for the digestion and absorption of food is apt to be better than in thin persons with digestive disorders. This capacity to absorb food products is very important to the diabetic, for it enables him to compensate the loss of sugar by eating and digesting an abundant supply of food. Where chronic digestive disorders exist the loss of sugar by the urine cannot be made good in this way, and the patient is liable to fail rapidly.

We may summarise as follows with reference to the outlook for diabetic patients :—

A mild form of the disease is indicated by (*a*) a fair and increasing assimilative capacity for carbohydrates, (*b*) the absence of organic acids in the urine, (*c*) an onset after the fiftieth year, (*d*) an inclination to obesity, (*e*) a vigorous digestion.

A serious type of the disease is indicated by (*a*) persistently low assimilative capacity for carbohydrates, (*b*) a considerable and increasing amount of organic acid in the urine, (*c*) onset during childhood or adolescence, (*d*) rapid loss of weight, (*e*) the occurrence of severe forms of diabetes in persons closely related.

It seems hardly necessary to remind you that the ability and willingness of the patient to take suitable care of himself has much to do with the prospects for the prolongation of life.

The treatment of diabetes involves a careful adaptation of the diet to the individual requirements of the patient, and makes necessary a consideration of habits of life, with special reference to exercise, rest, out-of-door occupation, mental and emotional strain, &c. Although treatment resolves itself largely into hygienic procedures, the question of using drugs has to be considered in many cases; and recently there has been added to the list of therapeutic measures the use of preparations of pancreas in the hope of supplying the organism with a missing internal secretion. Let us inquire very briefly what therapeutic results may be expected from the different means of treatment.

As you are doubtless aware, a diminution in the carbohydrates of the food is almost regularly followed by a diminution in the excretion of sugar, or, indeed, by its entire

disappearance from the urine. In some instances a moderate restriction in carbohydrate food is quickly followed by the disappearance of sugar from the urine. In other cases, withdrawal of the carbohydrates is necessary to bring about this result, and in still other patients this exclusion of sugars and starchy food fails to check completely the glycosuria. This abolition or subsidence of glycosuria, after restriction in carbohydrates, is the key to the dietetic treatment of diabetes. We restrict the carbohydrates in proportion to the severity of the diabetes, or, more accurately, in proportion to the patient's disability to utilise this class of food-stuffs.

A transient diminution in the amount of sugar excreted does not necessarily indicate that the condition of the diabetic has changed for the better, though it is possible that the corresponding reduction in the sugar content of the blood spares the organism from some toxic effects of this sugar. But the restriction of carbohydrates commonly leads to a result of much more importance than the mere temporary diminution in the sugar excretion. It leads to an increase in the capacity of the cells of the body to burn sugar. This is shown by the fact that a diabetic whose sugars and starches have been restricted for a time becomes able to take an increase in carbohydrate diet with a smaller loss of sugar by the urine than had been the case previously to the restriction and on the same diet. Another highly important result of such restriction is a reduction in the quantity of oxy-butyric acid which is excreted. I have noticed such a reduction in every instance where a patient was suddenly deprived of carbohydrates.

For the sake of convenience we may somewhat arbitrarily divide our diabetic patients into three classes. We have, first, the mild cases—that is, the cases in which a moderate restriction in carbohydrates is followed by a complete disappearance of sugar from the urine. It is not necessary to insist on extreme restriction. In elderly persons, where there is often little liability to an increase in the severity of the disease, it is only necessary to check the more gross errors of diet by the exclusion of potatoes, bread, pastry, &c. It is not always desirable to resort to a diet which completely removes the sugar from the urine, especially if such a diet is attended by a loss of strength. In the case of young persons, where there is considerable

liability to develop a severe form of disease, it is necessary to practise much more severe dietetic restrictions.

In order to feel certain that we are really dealing with a mild form of diabetes, it is necessary to test the tolerance of the diabetic from time to time. I say from time to time because it is a well-recognised fact that the tolerance is apt to vary considerably at different periods.

In the 'mild' type of diabetes it requires the addition of 60 to 90 grams of bread daily to a diet consisting of 1 litre of milk, 200 grams of proteid (eggs and meat), and 110 to 135 grams of fat, in order to cause glycosuria. To make this test satisfactory it is necessary that the patient should have been for five days previously upon a diet almost free from carbohydrate food, and previously to this for a few days on a diet containing only a moderate amount of carbohydrate material.

In the second set of cases—namely, those of moderate severity—a very considerable or complete deprivation in carbohydrate is necessary to free the urine of sugar. Here we are compelled to greatly curtail the use of sugar and starch-holding food. Experience teaches us that it is best to bring about this curtailment in a particular manner. Two or three times in the year these patients are wholly cut off from carbohydrates for three weeks. During the intervals they are permitted a moderate amount of carbohydrate food on condition that they practise a three days' fast from such food every two or three weeks. These alternations afford the best opportunity for an improvement in the assimilative capacity of our patients.

In the third set of cases, where the utmost practicable exclusion of carbohydrates fails to free the urine of sugar, the prospect is 'dubium ad malem vergens' under any known form of treatment. The urine in these cases usually contains a large quantity of organic acid, and we have the element of an acid intoxication to keep in mind. But, in spite of the bad prognosis in most of these patients, we can probably do something to prolong life a few months, or even years, and render existence more comfortable by minimising the liability to complications. It is necessary to be strict in regard to the use of carbohydrates, but it is unwise to completely exclude these foods, because such rigid restriction impairs the appetite and strength of the patient. A small amount of easily digested carbohydrate food is

therefore permitted most of the time. The Huntley & Palmer breakfast biscuit, peas, string beans, and milk give us this food in the most available form for diabetics. But it will not do to allow your patients to continue uninterruptedly on even a small allowance of carbohydrates. It is wise to practise the utmost restriction in such foods three or four times each year during a period of one month. This is done in the hope of improving the tolerance of the patient for carbohydrates. Sometimes this hope is realised; often it is not.

I cannot impress on you too strongly the necessity for individualising in the treatment of your diabetic patients. It is necessary to determine the assimilative capacity of each patient for carbohydrates, not once but many times, in order to obtain the best results from dietetic regulations. The main indication is to reduce the glycosuria and the organic acids at the same time that the strength of the patient is husbanded. It is easy to err in the direction of excessive restriction of the carbohydrates in following too zealously the aim of doing away with the glycosuria. This mistake was very common in the middle of the last century. To-day the tendency appears to be in the opposite direction, and the results are equally disastrous. We must steer a middle course if we would avoid both Scylla and Charybdis, but there are no hide-bound rules to guide us in this difficult course.

The form of carbohydrate food which is best assimilated by diabetics varies somewhat with different individuals, and in every severe case an effort should be made to ascertain individual peculiarities. In most persons starch contained in green vegetables seems to be the most readily burned variety of carbohydrate. Usually lævulose or fruit sugar is much better utilised than dextrose—at least for a period. This fact can often be utilised in treatment. Milk-sugar and cane-sugar are commonly better burned than dextrose, but not so well as lævulose.

The fact that lævulose is better tolerated than dextrose is a fact of considerable theoretical interest, although we do not understand its significance. We know that certain varieties of yeast will decompose one kind of sugar and leave untouched the molecules of other varieties, much as a particular key will turn one lock but not another. This fact suggests to us that there may be a somewhat analogous explanation

of the behaviour of the cells to dextrose and lævulose. The remaining hypothetical ferment of the hypothetical internal secretion of the pancreas may conceivably enable the cells to act on lævulose but not on dextrose.

I have repeatedly mentioned the necessity for restricting the carbohydrates of our diabetic patients, but have said nothing about the replacement of the caloric energy of which the organism is thus deprived. In health an adult man eats, let us say, 400 grams of carbohydrates daily, yielding 1,640 calories gross. If we restrict him to 100 grams of carbohydrates we cut off 1,230 calories, which, of course, must be replaced. Experience teaches us that we can best replace the greater part of this by fat, and a smaller portion of it by means of an increase in proteid. The addition of 100 grams of fat to the diet would furnish about 950 calories. The addition of 100 grams of proteid would yield 410 calories. Thus the substitutions would more than compensate the loss of caloric energy from the carbohydrate restriction. In the severest cases of diabetes we may be compelled to replace the carbohydrates by proteids and fats to even a greater extent than in the case just mentioned.

Patients often tire of the use of so much fat in the diet. We can, however, replace fat in a measure by alcohol, and I consider this one of the most rational indications for the use of alcoholic preparations. The high caloric value of alcohol (8·5 large calories to the gram) is here very serviceable. Sixty grams daily—a very moderate quantity where gastritis does not exist—would give about 510 large calories; a not inconsiderable portion of the requirements for the day. Clinical experience gives support to the practice of using alcohol in severe forms of diabetes, and it has often been observed that the fats are more palatable where alcohol is used—a circumstance which can be turned to good account.

It is of great importance in every case of diabetes to insure to the patient an out-of-door life, physical exercise adapted to the individual needs, and freedom from worry. It is also more than ordinarily important to keep the skin scrupulously clean in order to guard against the infection to which diabetic patients are so liable.

At the present time we have little to expect from the use of drugs in the treatment of diabetes. Many remedies have been put on the market with testimonials as to their

almost miraculous efficacy. We have arsenauro, glykosolvol, saccharosolvol, antimellin, vin uranê Pesqui, and many others, but it will not do to overlook the fact that in the cases where great improvement or 'cures' have been claimed we either know nothing about the dietetic conditions or we know that the carbohydrates have been much restricted. The efficacy of an anti-diabetic drug must be judged by its power to diminish the excretion of sugar while the diet remains unaltered. It cannot be denied that some drugs fulfil this important condition in some cases. Opium and its alkaloids, antipyrine, salicylic acid, and jambul, are capable of diminishing the glycosuria of some patients. The effects of morphine and codeïne have been most carefully watched, and it is undeniable that a noteworthy reduction in the glycosuria is often observed even in some of the most advanced cases of diabetes. It is possible that this effect is referable to the diminution in the intensity of nitrogenous metabolism observed under the influence of morphine, but I am inclined to think the effect on the glycosuria is sometimes too considerable to admit of this explanation. The influence of salicylic acid is perhaps due to its action in modifying bacterial activity in the intestinal tract, but on this point we cannot speak with confidence.

Alkaline salts have been extensively used in the treatment of diabetes by means of various mineral waters. The use of such waters seems specially indicated in gouty persons. It is not clear that they are of use in the ordinary forms of diabetes. There is, however, one set of cases in which the use of alkalis is strongly indicated. These are the cases of diabetes in which the patient is in coma or in a condition where coma seems imminent. Indeed, we may say that the alkali treatment should be instituted wherever the ammonia excretion is increased.

I have already called your attention to the fact that in the acid intoxication of diabetes the blood and tissue cells are ultimately robbed of their alkali. This being the case, it naturally occurs to one that the introduction of alkalis would have a certain therapeutic value owing to the neutralisation of the acid or acids which threaten to reduce the alkalescence of the blood. Experimentally it has been found that rabbits poisoned by hydrochloric or other acid are quickly brought out of danger of death by the intravenous infusion of alkaline carbonates. In the human subject it

has been found that the excretion of ammonia by the urine can be very greatly decreased by the internal administration of sodium bicarbonate or sodium citrate. This, of course, means that the sodium enters into combination with the organic acid. In the case of the bicarbonate the displaced carbon dioxide finds its way to the lungs and is liberated there ; on the other hand, the ammonia of the tissues which had previously been diverted from the formation of urea, being no longer required for the neutralisation of acid, is now able to reach the liver and undergo the physiological conversion into urea. But the alkali which we administer does more than this. It also spares the calcium, magnesium, sodium, and potassium, of which the organism is being deprived in severe cases of diabetes. In saving the sodium and potassium we spare the materials required to re-establish and maintain the alkalescence of the blood. It is on this saving of the sodium and potassium of the blood that the therapeutic effect of the alkali treatment depends.

In order that the alkali treatment of diabetic coma should prove successful it is essential to employ large doses of the alkaline salts. The organic acids, on which the reduction of alkalescence depends, are produced in large amount, and continuously, by the cells of the organism. In order to neutralise this acid, even temporarily, we must use our alkalis freely. Probably the best treatment consists in making daily one or two intravenous infusions of a 2-per-cent. solution of sodium bicarbonate in a ·6-per-cent. solution of sodium chloride. The quantity introduced should be 1 or $1\frac{1}{2}$ litre at each infusion. Five grams of sodium bicarbonate should also be administered every two hours during the day and night. If we use less alkali we can hardly expect to cope with the intoxication. Even with the large quantities of alkali just mentioned success is not assured, but in many instances the introduction of the alkali is followed by a rapid restoration of consciousness. I am strongly disposed to believe that the failure to see improvement after infusion has often been due to the use of insufficient amounts of alkali.

But even at best the alkali treatment of coma is only palliative. The infusion of alkaline salts does not check the production of acid or increase its combustion ; it merely neutralises the acid which is acting harmfully on the alkalescence of the blood. We may delay death a few days, or

weeks, or possibly months. More than this we cannot expect until we find some way of modifying the activity of the cells, so that they are able to burn the organic acids, or until we discover some method of checking the excessive production of acid.

The advent of coma can, I believe, always be predicted by a study of the urine. The alkali treatment should be commenced long before the onset of actual coma in all cases of diabetes which show a large excretion of organic acid. In addition to this the contents of the intestine should frequently be evacuated by means of castor oil or salines. Free catharsis in the ante-comatose stage of acid intoxication has a remarkable effect on many symptoms such as dizziness, headache, and restlessness. The phenomena of marked improvement in these cerebral symptoms under the influence of cathartics suggests that the state of bacterial activity in the intestine and of food absorption bears an important relation to the acid intoxication.

The therapeutic use of the pancreas in diabetes is based on the view that the disease depends chiefly on the defect of an internal secretion furnished by this gland, and that this secretion can be furnished to the organism by introducing the pancreatic tissue of animals into the digestive tract of the diabetic. In view of the highly notable results obtained in the treatment of myxœdema by the use of the thyroid gland, it is perhaps not surprising that somewhat analogous effects should be hoped for in diabetics fed on pancreas. The results have, nevertheless, been disappointing. The pancreas has been administered sometimes as the gland itself, sometimes as a glycerine extract, in a considerable number of cases of diabetes. Some improvements and some cures have been claimed, but it is quite evident that the practical results obtained up to the present time do not justify the hopes originally entertained. More experience is certainly required to definitely settle the value of this method of treating diabetes, but I confess much scepticism in regard to it. There is no evidence that the administration of pancreas or its extracts really increases the ability of the cells to burn sugar. I do not think this inconsistent with the doctrine of the pancreatic origin of diabetes, for we have no right to expect the hypothetical ferment of the pancreas to pass uninjured through the digestive tube into the blood, and ultimately reach the cells where it is needed to aid in

the combustion of sugar. Even the subcutaneous injection of the hypothetical ferment, could it be isolated, might fail to reach the right cells under the right conditions to do what was hoped for. In one direction the internal use of the raw pancreatic gland has shown itself to be highly efficacious. This is in effecting the subsidence of the steatorrhœa, or fat diarrhœa, which is present in those cases of diabetes in which there is advanced atrophy of the pancreas, and hence a defective secretion of pancreatic juice. But on this subject I have already said enough in another connection. (Lecture VIII.)

Thus one has to admit that in the treatment of diabetes, we have, at present, to rely mainly on carefully and individually adjusted hygienic measures, of which diet is by far the most important. We can hardly hope to do more than we are doing now until we know more about the real nature of the disturbed cell activities which lead to the failure to burn sugar. This is only another way of saying that we must see deeper into the nature of the oxidations carried on by cells before we can even hope to establish a curative treatment of diabetes.

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LECTURE XIII

STARVATION, UNDER-NUTRITION, AND OBESITY

Acute starvation and chronic inanition or under-nutrition—The subject of acute starvation lives on his own cells and fluids—Activity of metabolism in the first days of hunger—Metabolic characters of prolonged hunger; loss of weight and diminution in the intensity of cellular activities—Excretion of nitrogen—Combustion of proteid and fat in starvation; relative caloric yield of these nutritive materials—Respiratory quotient is lowered in starvation—Duration of inanition compatible with life—Change in metabolism after consumption of the fat of the organism—Temperature in starvation—Influence on the digestive tract—Diminished activity of the digestive secretory glands—Persistence of the putrefactive processes—Influence of starvation on the blood—Changes in the composition of the urine—Diminished excretion of the chlorides—Excretion of the phosphates and sulphates—Acetone and organic acids—Recapitulation—Clinical states attended by acute starvation—Chronic inanition—Marasmus in children—Wasting from fever; from malignant disease—Causes of chronic under-nutrition—Resemblances and differences between acute starvation and chronic under-nutrition—Nitrogen excretion—State of the digestive tract—Excretion of salts—Degree of emaciation compatible with life—Reconstructive processes—Treatment—Normal and pathological accumulation of fat—Origin of fat—Obesity results from disproportion between combustion of fat and use of fat-making food—Free use of fat-making food does not always lead to obesity—Effect of impaired digestion—Effect of muscular exercise—Effect of cold—Inherited susceptibility to obesity—Respiratory exchange in fasting state; during digestion and absorption; during exercise—Effect of restricting diet—Resemblances between diabetes and obesity—Diet and exercise the basis of treatment—Influence of thyroid on metabolism of the obese—Restriction of fluids—Effects of catharsis.

THERE are certain topics closely connected with the chemical pathology of digestion and metabolism of which it is important that I should speak to you before concluding this winter's course of lectures. I have in mind especially the subjects of starvation, marasmus, and obesity.

In the practice of medicine we frequently meet with nutritional disorders that are the result of starvation. Usually the inanition is not complete, for it is only seldom that patients are so conditioned that they absorb no food from the digestive tract during a considerable period of time. But the nutriment absorbed is often so slight in amount that a considerable or even extreme degree of emaciation results. It may be that the patient is taking into his stomach a considerable quantity of food, and that the impaired nutrition depends more on disturbed absorption than on a want of food. Cases of this sort are especially apt to be misleading, and it is only by keeping in mind the pathological characters of inanition that you will be enabled to recognise the nature of such cases from the character of their metabolism. I will give you an example of what I mean. A patient suffering from repeated vomiting and constipation grows gradually very thin and becomes bed-ridden from want of strength. You find the vomited matters contain little or no free hydrochloric acid, and although no abdominal tumour can be felt, you suspect cancer as the cause of the emaciation. You examine the urine and find it contains only a trace of sodium chloride. Then you know that the patient's loss of weight and strength is due to inanition, although he takes considerable food. The loss in weight does not require us to suppose that it is due to the cachexia of malignant disease, for it clearly depends on the repeated vomiting. The vomiting probably depends on a stenosis of the pylorus, and this may or may not be malignant in character. Without knowing the state of the chlorine elimination we might hesitate to refer the failure in nutrition to the occurrence of vomiting.

It is important to make a distinction between acute starvation and states of chronic inanition. The former condition has been carefully studied by modern methods of research, and has taught us much. States of chronic inanition have received less careful attention, though they are of more practical importance to the clinician. Let us consider, first, the chemical pathology of acute starvation.

Acute starvation is produced by the sudden withdrawal of all nutriment from a person who has previously been well nourished. The essential feature of the condition is that the subject lives on his own cells or on nutrient materials stored in his own cells and fluids. Nutrient

material, such as the fat in the cells and the proteid in the plasma or lymph, now begins to be used. The subject of acute starvation also uses very largely the protoplasm of his muscles as materials for the maintenance of oxidative and other processes essential to life.

In the first days of acute hunger the activity of the metabolic processes is little below that on a full diet. Thus in a classical experiment the caloric expenditure of the subject was 2,362 calories in twenty-four hours in a state of rest and while taking food. Under the same condition, but in starvation, there was a fall to 2,320 calories. This slight difference in caloric expenditure may be regarded as corresponding to the caloric requirements of the digestive glands, which cease to functionate during complete starvation. Since the activity of metabolism as indicated by the heat production is so little reduced in the early days of starvation, one would expect to find the daily intake of oxygen and the daily excretion of urea to be little altered. This is in fact the case.

With the prolongation of the period of hunger the general metabolism becomes modified by the influence of two factors: first, the loss in weight, and second, a slight but distinct reduction in the intensity of certain vital activities. The loss in weight during starvation depends on the consumption of unreplaced proteid and fat in the body-cells and on the loss of water and salts. In most instances of experimental starvation the subject has been permitted to take water. Without this use of water the loss in weight would be far greater. But even when the subject is not restricted as regards water a loss of weight is soon perceptible. This loss amounts to about 1 or 1·5 per cent. of the body-weight each day. You can readily see that after the lapse of a week or ten days of starvation there is a sufficient diminution of cell-substance to give rise to a distinct reduction in the total heat production each day and to a marked decrease in the excretion of urea, even were destructive metabolism to proceed with the ordinary intensity. The breaking down of the cells proceeds, however, at a somewhat diminished pace. Consequently we see a diminished caloric expenditure per kilo, and also a diminished excretion of nitrogen. For example, it has been estimated by Von Noorden that the caloric loss in a normal well-nourished man amounts to about 34 calories per kilo, while that of a starving subject is 30 to 32 calories per kilo.

The combination of the loss in weight and the diminution of cell activity per kilo occasions a considerable diminution in the output of nitrogen per day, this excretion occurring chiefly in the form of urea. Thus the results obtained from the study of the professional starvers Cetti, Breithaupt, and Succi justify the conclusion that the total loss of nitrogen per day by the urine amounts to about 9 grams during the first days of starvation. This is equal to a little more than 18 grams of urea. The normal quantity, however, of urea excreted in health by men of average weight is from 25 to 30 grams or even more. If we include the nitrogen lost by the fæces, the daily loss of nitrogen in each case would be somewhat higher.

I wish you to notice that although there is thus a marked fall of the nitrogen output in the early period of starvation the quantity lost is by no means inconsiderable. Ten grams of nitrogen lost by the urine represent 625 grams of proteid. There are cases of disease accompanied by acute starvation in which the loss of nitrogen is much greater, but this is probably owing to the action of protoplasmic poisons, which give rise to an excessive destruction of cell material. Acute phosphorus poisoning is a typical example of a state in which such excessive destruction occurs. One may suspect the activity of a protoplasmic poison whenever the destructive metabolism is distinctly increased in the early stages of starvation.

In the later stages of inanition we see a still greater falling off in the nitrogen excretion. This is due partly to the increasing loss of weight and partly to the diminution in the intensity of metabolism. In one case the nitrogen excretion of a male patient fell to 4·417 grams in twenty-four hours on the twenty-eighth day of the fast. The nitrogen excretion per kilo. in this case equalled 0·085 gram. Here the nitrogen loss per kilo was very low indeed compared with the average output from the first to the tenth day of abstinence, which was about 0·15 to 0·23 per kilo. Other observations of a similar tenor are recorded. In women the nitrogen excretion falls even lower than in men, owing probably to the smaller weight of the body. In one adult female the nitrogen excretion fell to 2·794 grams in the twenty-four hours from the fifteenth to the sixteenth day of inanition.

I wonder whether it has occurred to you to ask what

substances in the body supply the greater part of the fuel for combustion during a state of inanition. The question is one of considerable interest, and can be readily answered. The body contains at least three kinds of combustible material which might be drawn on in starvation—proteids, fats, and carbohydrates. In starvation the supply of carbohydrate material is soon exhausted, as is shown by the very great reduction of the glycogen in the liver and muscles. The organism must therefore live on its proteids and fats. In what relative proportion are these two constituents of the organism taxed? There are two facts which enable us to determine this for every case. First, a knowledge of the nitrogen excretion; and second, a knowledge of the caloric expenditure for the twenty-four hours. The nitrogen output by the urine gives us the quantity of proteid which is broken down, since 1 gram of nitrogen equals 6·25 grams of proteid approximately. It also gives us the heat value of the proteid consumed. But as we know the total expenditure of heat in the twenty-four hours we can readily calculate how much fat it would require to make this good. An example will make this clearer. A man with abundant adipose consumed 50 grams of his own proteids on the second day of starvation. This was calculated from the nitrogen excretion. These 50 grams of proteids yielded about 205 calories. Now the total caloric expenditure for the day was 2,102·2 calories; in other words, this man obtained caloric energy equal to 1,897·2 grams from the consumption of his fat. In another instance a lean patient consumed 88 grams of proteid, with a value of 360·8 calories. But the total caloric loss having been 1,848·8 calories, 1,488 calories must have been derived from fat. You perceive that in the first case 90·3 per cent. of the caloric energy was derived from fat; in the second, 80·5 per cent. It is thus clear that even in lean persons by far the greater portion of the energy expended in carrying on the various processes of life comes from stored fat. It is a significant thing that the fat-like substance in the nervous system, which exists there in abundance as the compound of phosphorus which we know as lecithin, does not suffer materially in starvation. Perhaps this is one reason why important nervous functions may be little impaired even in advanced cases of starvation.

The circumstance that a starving man lives on his fats

and proteids explains a well-established peculiarity in the respiratory exchange of gases—namely, that while the intake of oxygen is not diminished per kilo weight in starvation the output of CO_2 is diminished very distinctly. As the physiologists say, the respiratory quotient is lowered. This depends on the fact that the same quantity of oxygen burns very different quantities of the three leading foodstuffs.

Thus :—

100 grams of O_2 burns 35 grams of fat to $CO_2 + H_2O$, with a yield of 325 calories.

100 grams of O_2 burns 84·4 grams of carbohydrate to $CO_2 + H_2O$, with a yield of 346 calories.

100 grams of O_2 burns 74·4 grams of proteid to $CO_2 + H_2O$ + urea, with a yield of 362 calories.

It is clear from these facts that, on theoretical grounds, we should expect a much larger yield of CO_2 as a combustion product where carbohydrates are used as food than where they are not. Careful physiological experiments show that on an abundant carbohydrate diet the respiratory quotient $\left(\frac{CO_2 \text{ formed}}{O_2 \text{ used}}\right)$ is not far from 1. On the other hand a person on a proteid diet has a respiratory quotient not far from 0·73, and on a diet chiefly of fat a quotient of about 0·70. In starvation the respiratory quotient is usually 0·70 or less ; that is to say, the respiratory gas exchange behaves as it does in persons on a diet of proteid or fats. This is exactly what we should expect.

In starvation the respiratory quotient has been known to fall as low as 0·50. There is only one way to explain such a figure as this—namely, on the supposition that it is owing to the accumulation in the blood of unburned carbon-holding substances.

How long is it possible to prolong inanition without lasting impairment of health or danger of death ? Fortunately cases of absolute starvation for such long periods are extremely rare, except as the result of deliberate experiment. The professional Succi starved thirty days without serious after-effect. Merlatti and Tanner are supposed to have starved forty and fifty days respectively, but we are not certain that their fasts were absolute. As regards the loss in weight that is consistent with human life, we cannot give a wholly satisfactory answer. It is estimated, how-

ever, that death from acute starvation could not be long delayed after the patient had lost one-third of his original weight

I think you can understand that we should expect a very important alteration in the character of metabolism after the fat of the body has been nearly or wholly consumed. Such a complete consumption of fat would necessarily lead to a state of metabolism in which all the heat expended would have to be furnished by the destruction of proteid. This leads to an enormous terminal increase in the excretion of nitrogen. I am not certain that this condition has been observed in human starvation.

The temperature of the body remains normal in acute starvation or is only slightly depressed. This harmonises well with the fact that the oxygen utilised by the body per kilo weight is not lessened, and that heat production is little impaired. We should of course expect the temperature to be maintained at the normal level on purely *à priori* considerations, since it is well known that any considerable and persistent lowering of this temperature is incompatible with the maintenance of those oxidative processes which are essential to life. In animals that are starved to the point of death the temperature falls considerably in the last hours or days of life. A similar fall you will sometimes observe in the course of chronic inanition. In experiments on animals life has been considerably prolonged by placing them in a warm chamber after the body temperature has fallen.

Having now sketched for you some of the more general features of the deranged chemistry of acute inanition, I wish to say something of certain effects which show themselves in the digestive tract, in the blood, and in the urine. As medical practitioners it is important for you to be acquainted with most of these facts.

The condition of starvation induces distinct alterations in the state of the digestive tract. In the absence of food there is a marked and persistent decline in the secretory activity of the digestive glands. Salivary secretion is reduced even when water is abundantly used, and its diastatic ferment is diminished in amount. The diastatic action appears, however, not to be entirely lost. The interesting observation has also been made that during starvation there is a considerable increase in the quantity of this ferment in the urine. Probably much of this ferment comes from the

pancreas, which like the salivary glands pours little secretion into the digestive tube. As might be expected the gastric juice shares in the general depression of secretory function. Prolonged inanition leads to a minimal secretion of free hydrochloric acid and pepsin. This depressant effect on secretion may last for a long time after the termination of the fast. Although there is thus a marked diminution in the secretory activity of the gastric glands, this appears to be chiefly owing to the absence of the normal stimuli to activity, since with the introduction of food there is usually a prompt if not adequate secretory response.

The behaviour of the bile and of the succus entericus differs from that of the secretions I have just mentioned Although somewhat reduced in starvation they continue to such an extent as to indicate that they possess an excretory significance. Direct observation of the bile in starving dogs shows a gradual sinking in the volume of the secretion with increasing concentration and only a moderate decline in total solids. Similar researches in the human subject are of course impossible, but there is satisfactory indirect evidence that the bile continues to be secreted in considerable amount. This evidence consists in the fact that the urobilin of the urine is only slightly diminished in starvation. As I have already told you in speaking of the liver, urobilin comes only from the transformation of bilirubin. Bilirubin continues to be formed because of the continued destruction of red blood-cells.

That the succus entericus continues to be made in the course of starvation is rendered probable by the continued appearance of fæces. In the case of one professional starver 220 grams of moist fæces, containing 38·2 grams of dry substance, were passed in the course of ten days. This fæcal material contained an amount of nitrogen equal to 0·2 gram of nitrogen per day and an amount of fat equal to 1·34 gram. It is supposed that this not inconsiderable quantity of fat is derived from the glands of the intestine.

You may perhaps think that in a state of starvation the putrefactive processes in the intestine are greatly reduced or altogether extinct owing to the absence of proteid food. Putrefaction, however, continues fairly active even in prolonged starvation. It has been observed in men that the indican reaction may persist after many days of inanition, and it is exceptional for it to disappear in fasting dogs.

There is nevertheless a disposition for the indican to grow less in amount, and its complete disappearance has been noted after a few days of starvation. On the other hand, phenol in the urine is almost regularly increased to a considerable extent after an initial fall. The ethereal sulphates continue to be formed to some extent, as one might expect where phenol is excreted in large amounts.

From these facts it is evident that putrefaction in the intestine persists during starvation, but that the character of the putrefactive decomposition is different from that of health, as may be inferred from the increased formation of phenol. It is not very difficult to understand why putrefaction continues, for, as I have explained to you, the fæces contain nitrogenous materials fit for putrefactive decomposition. Nor is it singular that the character of the decomposition is not the same as that observed in well-fed subjects. The proteid intestinal contents during starvation consist chiefly of nucleo-albumins and mucins derived from the bile and from the epithelium of the intestinal tract. From these bodies we should reasonably expect cleavage products different from those in the case of intestinal putrefaction from food. Whether the bacteria undergo important changes in their life activities is not certain, but it is not unlikely that these activities undergo some modifications.

Certain interesting facts have been worked out in relation to the blood during starvation. The observations that have been made regarding the percentage of solids and the numerical relation of the red cells to the volume of the plasma indicate that the blood undergoes little change in these respects. In some instances of starvation there is a slight increase in the concentration of the blood and an apparent increase in the number of the red blood-cells. You know that in normally fed persons the withdrawal of water is followed by a distinct concentration of the blood. It naturally occurs to one that the augmented concentration of the blood during inanition depends on loss of water. It is, however, not entirely clear that this is the case.

That the leucocytes are distinctly reduced during starvation is certainly of considerable physiological interest, though we do not know its full significance. In the case of Succi there was a gradual fall from 14,530 to 861 white cells in the cubic millimetre during the first seven days of starvation. Then for twelve days the number remained about 1,000, and

showed a slight rise at the very close of the period. In other instances the fall has been less decided. In a starving dog I observed a fall to about one-half the normal number of leucocytes. What is the meaning of this diminution in leucocytes? It seems reasonable to think that it depends rather on a diminished formation of white blood-cells than on increased destruction, for in the latter case we should expect to find the uric acid and xanthin derivatives of these cells increased in the urine, which is not the case. It seems likely that the diminished destruction of leucocytes in starvation is related to the removal of certain physiological stimuli to cell multiplication that are furnished by the food, perhaps especially by the proteid foods.

As to the character of the leucocytes in starvation we know little. In a fasting dog which was observed in my laboratory the proportion of lymphocytes to the polymorphonuclear elements was distinctly diminished, the total number of white blood-cells showing a diminution.

There are two additional facts about the blood in starvation which it is desirable for you to remember. One is that the alkalescence undergoes no diminution. The other is that sugar continues to be present in the blood in an amount not greatly below the normal. At first sight it may seem to you singular that the blood contains sugar while the glycogen in the liver and muscles is so greatly reduced. These facts are, however, easily reconciled. In starvation sugar continues to be formed from the breaking down of proteid belonging to the cells of the body. If the breaking down of proteid is considerable, there is a correspondingly large yield of carbohydrate material. Hence the blood contains sugar. But this sugar is burned by the cells, and its quantity, though considerable, is never equal to the requirements of the organism. There is no chance for the liver or muscles to store glycogen because the body receives no carbohydrates as food, and all its sugar comes from the breaking down of the proteids belonging to the body-cells. The sugar in the blood is merely in transit for the use of those cells that split and burn the sugar molecule.

Many peculiarities of metabolism in starvation find expression in changes in the composition of the urine, and it is important that we should consider these with care.

Even where the subject of the fast is permitted the use of water, the volume of the urine is considerably below the

normal, falling usually to 700 c.c. or less in the twenty-four hours. This is owing to the circumstance that there is usually only a moderate desire for water. The output of water by the urine, skin, and lungs distinctly exceeds that taken with the drink. At first sight this might lead you to think there is a loss of water from the tissues, leading to an increase in the percentage of solid constituents. You must, however, bear in mind the fact that a large amount of fat is burned to carbonic acid and water, and, further, that this water prevents any loss from the tissues due to the difference between the water ingested and the water given off. The cells and fluids thus maintain very nearly their normal proportion of water. The case is different where the intake of water is greatly restricted. Here the cells gradually lose water and suffer in consequence in the manner I have already indicated to you in speaking of the uses of water in the organism. The urine then falls to a very small volume, and its specific gravity is correspondingly increased.

I have already told you of the nitrogen waste in starvation, and have little to add. You know that in health from 85 to 90 per cent. of the nitrogen is excreted as urea, about 2 per cent. as uric acid, much less than this as other xanthin bases, about 2 or 3 per cent. as creatinin, and from 2 to 6 per cent. as nitrogen of ammonia. These proportions undergo a slight shifting during starvation, owing chiefly to a diminution in uric acid and creatinin. The uric acid is usually distinctly diminished. With reliable methods I found it as low as one-fifth the normal in the human subject, and think it is usually at least somewhat diminished. I should not forget to state that some writers have found the uric acid increased, but it is likely that this result has been obtained through the use of inaccurate methods of determining uric acid, or was noted in patients not in a condition of absolute starvation. That the creatinin of the urine is diminished might be inferred on *à priori* grounds, for, as you have been taught, the muscle ingested as food is the important source of the creatinin of the urine. On the removal of this source of creatinin there is only one possible origin for this extractive, namely, the metabolic melting of muscle tissues. But, as I have explained already, the loss of muscle is not very rapid, and hence little creatin is excreted as creatinin. It has, indeed, been calculated that the amount of creatinin in the urine is just what would

be expected from the known extent of the muscle waste. The nitrogen of ammonia has not been sufficiently studied in starvation. In fasting dogs I have found it normal in amount. I believe that in uncomplicated starvation there is no increase in nitrogen of ammonia, because there is no acid intoxication, such an intoxication being, as I explained in the first lecture, the cause of an increased output of nitrogen in this form. Still it is conceivable that in the last period of starvation, where the body has only its proteid on which to live, organic acids find their way into the urine united to ammonia.

Let me now describe to you the alterations which occur in the excretion of salts during starvation. This subject has a considerable practical interest. We may first consider the salts from the standpoint of their acid radicals, and then from the standpoint of their basic radicals. We have, therefore, to speak of the chlorides, the phosphates, and the sulphates, and later of the calcium, magnesium, sodium, and potassium.

The marked falling off in the excretion of chlorides is one of the most striking features in the chemical pathology of starvation. The chlorides diminish rapidly in the first days of inanition, and soon amount to little more than a fraction of a gram in twenty-four hours. In the case of Cetti the chlorine sank from 5·5 grams on the last day of food to 0·6 gram on the tenth day of inanition. In one of my patients with stenosis of the pylorus the urine contained only about 0·12 gram for the day. Such low figures for the chlorides are only met in states of inanition and in a few febrile diseases, such as pneumonia and typhus. You are safe in making the inference that an adult patient without fever is suffering either from a great diminution in food absorption or from complete starvation, whenever the chlorides for the day amount only to a fraction of a gram. In my experience the inference permissible from the state of the chloride excretion has frequently been of practical service, because it has enabled me to form a judgment as to the amount of food absorbed.

Why is the state of inanition attended with such a decided fall in the excretion of chlorides? For the reason that the organism, even in starvation, always remains saturated with chlorides, and excretes only the chlorides in excess of the quantity held by the cells and fluids of the body. Now

there is only one source from which this excretable excess of chlorine can come in starvation, and this is in the metabolic melting of the tissues used for the maintenance of animal heat. I have explained to you that these tissues are chiefly fat and muscle. But the fat laid up in the body contains no chlorides, and the muscle contains only small amounts. A loss of nitrogen equal to 10·2 grams in a state of starvation represents the breakdown of about 300 grams of muscle, and 300 grams of muscle could yield only about 0·3 gram of chlorine. The nitrogen content of the muscle thus bears the proportion to the chlorine of the muscle of 34-1. As a matter of fact there are cases of starvation in which the excreted nitrogen and chlorine reach this ratio, as I have observed for myself. Thus you see that the low chlorine content of the urine is directly referable to the low chlorine content of the tissues consumed in starvation.

But very likely you will ask, How does it happen that the cells and fluids of the organism remain saturated with chlorides during inanition? I can give you only a superficial answer to this question. It is apparently a specific function of the kidney to remove salt from the blood when it reaches a certain grade of concentration, but when the salt content falls below this concentration the cells of the kidney apparently lack the necessary stimulus to effect the removal of the chlorine ions. Hence the sodium chloride of the fluids and cells never falls distinctly below the amount advantageous for the physical requirements of the organism.

The content of phosphoric acid in the urine of starvation is governed by the same kind of conditions that determines the quantity of chlorine excreted. In health the phosphoric acid is derived more largely from the normal metabolism and less from the food than is the case with the chlorides under normal conditions. In starvation the phosphoric acid, like the chlorine, comes wholly from the metabolic disintegration of tissues. Since the muscles and the cells of the glandular organs, like proteid material generally, contain an abundance of phosphorus, a considerable amount of phosphoric acid finds its way into the urine in the form of phosphates. The proportion of phosphoric acid to nitrogen is much greater than the proportion of chlorine to nitrogen because the tissues are so much richer in phosphorus than in chlorine. The proportion of chlorine to nitrogen in muscle is 1–34; of phosphoric acid to nitrogen, 1–7. If the

tissue melting of starvation were confined to the muscular and glandular organs, we should expect to find about 1 part of phosphoric acid to 7 of nitrogen in the urine. But observation shows that the proportion of phosphoric acid is distinctly greater, in fact reaches a ratio of 1–4 in some instances. Whence comes the additional phosphoric acid? It comes from tissues richest in phosphates, namely, the bones. The evidence of this is convincing. In the first place the urine during starvation shows an increase in the excretion of calcium. Indeed, the quantity of calcium eliminated is sometimes greater than in the period previous to the fast. Such amounts of calcium can come only from the bones. Then, again, the magnesium in the urine is present in the same proportion, relatively to calcium, as in the bones. I do not know whether direct observations have been made on the size and composition of the bones in human starvation, but in dogs there is a decrease in the amount of bone, especially in the long bones. I have noticed that the composition of the bones suffers little alteration from starvation, the quantity rather than the quality of tissue being affected.

The sulphates of the urine have the same origin as the nitrogen—namely, the decomposition of proteids. Hence there is, as one might expect, a certain parallelism between the nitrogen and the sulphur in the urine during inanition. The proportion of sulphur varies in different tissues more than does the percentage of nitrogen. Therefore the relation of sulphur to nitrogen in the urine varies somewhat with the character of the tissues that are being burned. Nevertheless during complete inanition the ratio of nitrogen to sulphur in the urine is not far from 16–1, or about the same as in proteid.

I have already told you something about the behaviour of calcium and the magnesium during starvation. It is not necessary for me to go into further detail in regard to the elimination of these bases. Nor is there much of importance to say in regard to sodium and potassium. The important thing to remember about these alkali bases is the reversal in their quantitative relations. In the urine of persons on ordinary diet the proportion of potassium to sodium is about 2–3, which corresponds roughly to the quantities found in the food. Now the cells and the fluids of the body contain much more potassium than sodium, the ratio being about

3–1 in the body ash. In starvation the new supply of sodium and potassium is cut off, and the sodium and potassium of the urine are supplied by the tissues themselves. We should naturally expect, therefore, that the proportion of the alkaline bases would approximate to the proportion characteristic of the tissues. This expectation is justified by the facts. Thus in the case of Cetti the ratio of potassium to sodium was 3–1 on the tenth day. With this reversal in the quantitative relations there is a marked diminution in the excretion of these metals.

A highly interesting feature of all cases of starvation is the appearance of acetone in the urine. I have already had occasion to say something regarding the chemical nature of acetone and the cause of its appearance in the urine of diabetes. You will recall that I told you the evidence indicates that acetone is present under conditions involving the destruction of proteid and fat. Whenever the body has to live wholly or largely on its own proteid and fat we find acetone in the urine, and this is doubtless the explanation of the findings in the case of starvation. Remember that the output of acetone is very greatly increased even on the first day of starvation, and that food containing carbohydrates quickly occasions a fall in its excretion.

Together with acetone the urine sometimes contains diacetic acid. The amount is small at first, but gradually increases. In some instances also β-oxy-butyric acid has been found, but chiefly in cases of very advanced starvation. The significance of these bodies during inanition is the same as in diabetes : they result from the impaired oxidation of the products of proteid combustion. Since the appearance of β-oxy-butyric acid indicates greatly impaired oxidative powers, it is always an ominous sign.

Having now sketched for you the leading features in the chemical pathology of starvation, it may be well for me to recapitulate. In acute starvation the organism lives wholly at the expense of its own cells. The glycogen stored in the cells is rapidly exhausted, and after this the heat and power expended by the body are supplied by fat and proteid-fat stored in various parts, and proteid from the cells of the muscles, glandular organs, &c. The energy yielded by the burning of these materials suffices to maintain an expenditure of heat not greatly below the normal, sustains the body temperature, and permits a high grade of oxidative activity

in the cells adapted to such work. Much the greater part of this energy comes from the burning of fats now removed from storage. The active transportation of fat from the fat depôts to the cells that are suffering from want of carbohydrate may lead to an excess of fat in the blood. The melting away of the proteids is necessary to the maintenance of life processes, and the sacrifice of muscle and gland cells supplies about one-fifth of the caloric needs of the body. The extent of this proteid sacrifice can be measured in an individual case by the loss of nitrogen through the urine. The proteid waste is also roughly measurable by the phosphoric acid and the sulphuric acid present in the urine. As the muscle cells, so poor in common salt, are the chief source of the chlorides of the urine, the chlorine of excretion sinks to a very low level—a level highly characteristic of starvation. The acetone, diacetic acid, and β-oxy-butyric acid of the urine appear to be likewise the expression of incomplete proteid waste. But although the fats and the proteids of the muscles and glands supply the necessary caloric energy to the emaciated body, the muscle and gland cells are not the only ones that suffer. The bones are called upon, for reasons at present obscure, to sacrifice a part both of their mineral and organic constituents. The mineral loss leads to the presence of a relative excess of calcium in the urine. This calcium is united to phosphoric acid. The phosphoric acid from this source accounts for the excess of phosphates in the urine above the quantity that is accounted for by the proteid waste. Thus the sacrifice of fat, muscle, gland, and bone continues until the subject has lost one-third or more of his original normal weight. Death soon occurs if the inanition be prolonged beyond this point. It is not unlikely that death ensues because of growing demands made on the nervous system. The cells of the regulatory and controlling mechanism, at first spared, are probably at last called upon to make sacrifices inconsistent with the maintenance of their all-important functions. The fact that the nervous system has lost only about 1 per cent. of its weight at the time of death from starvation does not appear to me inconsistent with this view, since it is well known that histological alterations take place in the ganglion cells.

It is rare to meet with acute starvation as a clinical condition; but occasionally we see it, and are called upon to check its debilitating consequences. Perhaps the clinical

state which most nearly resembles experimental starvation is that in which new-born infants refuse food, or for some reason get little or nothing from the mother. Practitioners have many times been puzzled to interpret the loss in weight, the prostration, and the constipation that accompany such a state of inanition, and occasionally a baby dies because the trouble is not recognised and corrected. In other instances the inanition is not absolute, but nevertheless forces the patient to live almost wholly on his own fat and proteid. Sometimes the condition comes from inappropriate feeding, as where infants receive food consisting almost wholly of carbohydrates; sometimes it follows acute gastritis or enteritis. I have seen a patient with ulcerative colitis in whom the loss of weight was as rapid as in acute experimental starvation, even though the disease was unaccompanied by fever. Any pathological state which induces persistent diarrhœa may have a similar effect. Persistent vomiting is sometimes a cause. Patients with melancholia sometimes eat little or nothing during many days. You will occasionally see a patient with advanced stenosis of the pylorus dying of acute starvation. The temperature in these cases is usually normal or subnormal. Sometimes we see a rise in temperature during the first days of life in babies that are underfed. It is not clear whether this elevation in temperature is really due to the state of inanition; but some close observers suspect that this is the case. When acute inanition develops in the course of a chronic malady, attended with great debility, delirium may develop even in the absence of fever. The recognition of the element of starvation will sometimes shield you from the error of supposing that a delirious patient has an intracranial lesion.

I propose now to consider the chemical pathology of chronic inanition. Under chronic inanition I include those states of prolonged impairment of nutrition that result in a distinct diminution in the weight and strength of the subject. As you can readily understand, there are all grades of this chronic impairment in nutrition. The milder forms of the disturbance are consistent with the performance of a moderate amount of work. Patients of this class, though thin and feeble, may go about and even manage to make a living. Their friends and relatives, alarmed at the emaciation, usually pronounce them the victims of pulmonary tuberculosis with that confidence which characterises the medical opinions

of some laymen. After the lapse of years, however, it becomes clear, even to the ignorant, that the condition is really a chronic impairment of nutrition due to quite different causes from tuberculosis. In time the state of the patient changes. Either the nutrition improves to such a point that the subject can no longer be classed as an invalid, or he fails so much as to become bed-ridden. If the failure in nutrition becomes so pronounced as to necessitate life in bed, the patient's case belongs to the class of serious chronic inanition which is known as marasmus.

It is especially to this latter group of cases that I invite your attention. Although such patients are not very uncommon, their condition has by no means received the study which it deserves. The study of the element of starvation in these patients is apt to be complicated by the persistence of the cause of the nutritional failure. Thus where the malnutrition occurs in the course of diabetes, or cancer of the stomach, or chronic enteritis, these underlying states may perhaps be responsible for disturbances in the bodily chemistry which are at present inseparable from the element of inanition.

Some writers are disposed to restrict the use of the term 'marasmus' to states of under-nutrition brought on by bad food and unhygienic surroundings. In young children it is by no means rare to see extreme wasting as the result apparently of bad feeding and deficient air-space, though it is very likely that what we call a feeble constitution distinctly predisposes to the nutritive failure. Some of these little patients do very well when we secure for them good food and abundant air. Others continue to lose weight and strength in spite of the improved conditions. These children often take a fair amount of food, and have movements of normal appearance. Still they go steadily downward and ultimately die. At autopsy the most striking feature is a pronounced fatty infiltration of the liver, resulting, as such livers always do, from the excessive deposit and diminished oxidation of fat carried to the hepatic cells from the adipose depôts. Sometimes we see indications of a chronic gastro-enteritis, but in these instances there have usually been more or less definite clinical indications of digestive derangement. In other cases the mucous membrane of the stomach and the intestines looks normal even on histological examination. It is difficult to see why the food is not utilised in these cases, unless the

nervous activities connected with the digestion and absorption of food-products are in a state of profound slumber.

You may restrict the use of the term 'marasmus,' if you wish, to cases like those I have just described; cases in which there are no well-defined structural lesions to account for the origin of the under-nutrition. But I think it is better not to use the term in this restricted sense. I prefer to apply the word to all advanced cases of chronic under-nutrition in which the wasting and debility result from derangement in nutritive function as distinguished from the action of protoplasmic poisons. As I shall explain when we come to talk about fever, the wasting which accompanies an elevation in temperature depends in part on deranged nutrition, in part on the action of bacterial poisons which cause a pathological destruction of proteid.

You should therefore exclude from the class of marantic patients all those in whom there is continuous fever. Whether you should also exclude cases of wasting associated with cancer is still a question. It has been supposed that the wasting and cachexia of cancer depend on some unknown poison produced by the cells belonging to the new growth. There is, however, no satisfactory evidence that this is so. In many instances at least, the wasting appears to be due to purely nutritional disturbances, as is indicated by the great temporary gain in weight which often follows an improvement in the state of digestion. I think we may tentatively include in the class of marasmus at least most cases of wasting from cancer unaccompanied with fever. In some instances of carcinoma connected with the stomach, intestine, liver, or pancreas, the cause of the wasting can be discovered in some clearly defined interference with the nutritive processes, such, for example, as follow pyloric obstruction or an impediment to the secretion of the bile or pancreatic juice.

It is exceedingly important that you should clearly recognise the different causes that lead to chronic under-nutrition of the severe type. If you fail to recognise the nature of the causes at work in particular cases, you will almost certainly fail both in your prognostic effort and in your treatment. Perhaps I can help you to group the causes of under-nutrition in such a way that they will be easy for you to remember.

In the first place it is convenient to separate the

conditions that are connected with the digestion and absorption of food from those related to the fate of the nutritive materials after they enter the blood, the lymph, and the body-cells; in other words, we distinguish between causes connected with digestion and causes connected with metabolism. Pathological states of digestion are by far the most common causes of chronic under-nutrition. In some instances the trouble lies in the pathological expulsion of the food from the body, as in states where there is persistent vomiting or persistent diarrhœa. In other cases there is an obstruction to the passage of the food into the intestine, which interposes a very serious mechanical obstacle to proper digestion and absorption. Still another group of patients are marantic because the food which they eat is decomposed in the stomach or gut through the excessive activity of micro-organisms. The result is that only a small part of the food is available for nutritive purposes. Such excessive fermentation and putrefaction of food occur whenever there is impaired secretion of digestive juices or defective absorption. Depression of the nervous system is a prominent cause of such secretory and absorptive disturbance. Then, again, the diversion of the food potential may be the consequence of pathological states, which cut off the bile or the pancreatic secretion through mechanical agencies. Thus you see that a patient may fall into a state of partial starvation through a variety of causes. The effect on nutrition is ultimately the same, whether the food be lost through vomiting or diarrhœa, or through the excessive activity of micro-organisms; in each case the organism loses a part of its nutritive potential, and is forced to live to some extent on its own tissues.

In the metabolic disturbances that lead to chronic under-nutrition the cells are for some reason unable to properly utilise nutritive materials, which are carried to them in the blood for the production of heat. Consequently the body is compelled to live on its own fat and proteid, with the inevitable loss of weight and strength. We see this in diabetes, where, as I have already told you many times, the combustion of sugar is greatly impaired. I do not know of any other purely metabolic derangement in which the utilisation of other forms of food material is similarly impaired.

It may possibly occur to you that the loss of serum albumen and serum globulin which occurs in the course of

renal disease may act detrimentally on the organism in a manner somewhat similar to the loss of sugar in diabetes. The resemblances, however, are superficial. In both instances, it is true, the body loses material which yields energy, and in both this loss of material may occasion serious results to nutrition. But in the case of the sugar loss the cells lose their carbohydrate food because they no longer possess the capacity to burn it; in the case of albuminuria the cells suffer from the loss of nutritive proteid, simply because there is a serious renal leak which cannot be fully compensated by the absorption of an increased amount of proteid material from the intestine.

In reviewing with you the chemical pathology of acute inanition I intentionally made no references to the chemical disturbances incidental to chronic under-nutrition. It is desirable, however, that you should know how such disturbances resemble the derangements of acute inanition, and also how they differ from them. This subject presents numerous difficulties to the investigator, and there are many points on which we are still ignorant. I shall bring to your notice some of the ascertained facts that are of practical interest.

One would naturally expect that the chemical processes carried on by a marantic individual should resemble in many respects the processes incidental to acute starvation, but one would also expect important differences, because of the much more gradual character of the cell wasting in the case of under-nutrition.

The destruction of proteid in marasmus may fall to a very low point, for the organism lives chiefly on its fat, as in acute starvation. Consequently the nitrogen output in the urine may drop to 6, or even 4, grams per day in an adult male. In cases where a fair amount of proteid food continues to be eaten the nitrogen excretion may amount to twice as much as I have mentioned, and this greater output is consistent with a high grade of emaciation. The excretion of uric acid often falls relatively more than the nitrogen of urea. In health the ratio between uric acid and urea is about 1–50; in marantic states it is often 1–80 or 1–100. The ratio may be normal, or the proportion of uric acid may be increased in cases where considerable food is being eaten. In marasmus the secretion of gastric juice is diminished, perhaps in a degree roughly proportionate to

the quantity of food taken. I do not know that careful studies have been made of the behaviour of the hydrochloric acid, but it is thought that the free acid is sometimes present even in advanced cases after food is given.

The pancreatic secretion probably suffers a similar reduction, but there is no definite knowledge on this subject. Putrefactive processes are almost always active in the intestines. Indican is usually found in abundance in the urine, and phenol is increased even where the indican is not. The state of the blood has not been carefully studied. There is usually increased concentration of the blood and a moderate reduction in hæmoglobin. An actual diminution in the number of red cells may be masked by an increased concentration of the plasma. The white cells are present in normal proportion to the red, or are somewhat diminished. I have known the leucocytes to drop to 2,500 in the cubic millimetre in a young girl who was underfed. It is not very rare to find only 4,000 or 5,000 leucocytes in poorly nourished hospital patients. A marked reduction in red cells, or a distinct increase in the number of leucocytes, is probably referable to complicating conditions, and not to the under-nutrition itself. There is no evidence that the alkalescence of the blood is diminished in states of under-nutrition. Sometimes organic acids are present in the urine, and from this it may be inferred that some degree of acidosis exists in such cases. But since the acids referred to are probably united to ammonium, it is unlikely that the sodium carbonate of the blood is called upon to neutralise the acid or acids. It is thus improbable that the alkalescence of the blood is altered. Some emaciated diabetic patients are, of course, an exception to this rule.

The volume, specific gravity, and reaction of the urine vary widely in different cases of chronic under-nutrition. Most frequently the urine is scanty and of high specific gravity, probably because patients with advanced marasmus drink less than persons in health. The sodium chloride excretion is variable, but is always low. This is an important point. Sometimes the usual relation to the urea of the urine is not changed, the proportion remaining about one part of sodium chloride to two or three parts of urea. In other cases there is a relative as well as an absolute reduction, and you can form some idea as to the extent of food absorption from the quantity of sodium chloride that reappears in the

urine. The amount may be so reduced as to indicate absolute starvation. The excretion of phosphoric acid in marasmus is influenced by many conditions, and does not help us to form an estimate of the degree of inanition. Usually it is not far from the normal, that is, one part of phosphoric acid to seven of nitrogen. As regards the sulphuric acid excretion nothing of practical importance is known. The calcium phosphate of the urine is said to be increased whenever nutrition is greatly impaired from any cause. It is unknown whether any of this calcium comes from the bones in states of marasmus falling short of absolute starvation. One is liable to meet with an increase of acetone in the urine whenever the proteid waste of the organism is abnormally large. Less often we find diacetic acid. The presence of a moderate excess of acetone is unimportant as regards the prognosis, but the presence of β-oxy-butyric acid is an evil omen.

There is an important difference between acute starvation and chronic under-nutrition as regards the degree of emaciation that is compatible with life. As I have already mentioned the subject of acute starvation is in danger of fatal prostration when he has lost about one-third of his normal weight. In chronic under-nutrition the cells apparently grow accustomed to even greater losses of substance, for it sometimes happens that we see a patient lose more than one-half his original weight. So great a loss in weight is not inconsistent with recovery. In making these statements as to the degree of emaciation consistent with life I have in mind a subject originally well nourished but not corpulent.

I regret to say that we are without satisfactory information as to the processes involved in the reconstruction of the tissues after great emaciation. Such knowledge might furnish us with important suggestions in the treatment of states of inanition. It is likely that there are important differences in the reparative processes after acute starvation and after long periods of under-nutrition. I hope we shall some day have careful comparisons between reconstruction in such conditions and the constructive processes as they occur in growing children.

At present we do not know just what principles should enter into the feeding of patients recovering from acute and chronic states of starvation. One fact, however, is clear. The subjects of acute under-nutrition accompanying any acute or

subacute febrile disease have cells that are eager to assimilate nutritive materials. If the stomach and intestine are not the seat of disease, these patients recover with surprising rapidity on a liberal diet representing proteids, fats, and carbohydrates. It appears not to make much difference in the rapidity of the nutritional convalescence whether there is an excess of proteid, or of fat, or of carbohydrate. The main requirement seems to be a quantity of food considerably in excess of the needs of the body. Then the cells are rebuilt with a retention of proteid, and fat accumulates rapidly in the fat depôts.

The case is entirely different where we have to deal with chronic under-nutrition. Here we not only have to contend with the difficulties incidental to the removal of the cause of the nutritional failure, but the cells concerned most actively with the nutritional processes have probably acquired bad habits of work, which call for their physiological re-education. The practical result is that even when such persons are placed under the most favourable conditions their recovery is apt to be tedious and uncertain.

I shall not attempt to formulate for you any plan of treatment applicable to marasmus generally; such an undertaking would be irrational. The plan of treatment and the prognosis must be separately worked out for each individual case according to the ascertainable causes of the failure in nutrition. These causes are so varied that the treatment in different instances varies widely. A marantic patient in whom you discover a stenosis of the pylorus, with great dilatation of the stomach, must be treated on different principles from one who simply has a long-standing chronic gastro-enteritis with occasional exacerbations. But, whatever may be the cause, it is necessary in each instance to inform yourself regarding the state of the digestive organs as regards size, position, and secretory activity, and as regards the occurrence of fermentative and putrefactive processes. Then, having satisfied yourself that there is no gross condition demanding immediate surgical interference, you will endeavour to discover and institute the rules for diet, rest, exercise, &c., that seem best adapted to the particular needs of your patient. To do this requires much thought and painstaking care.

I wish now to speak to you of a subject not less interest-

ing than the state of inanition which we have discussed, The state of obesity, or excessive fatness, is one that has long attracted the attention of physicians, and speculations as to its nature fill many a treatise. In recent years the condition has received some attention from investigators equipped with modern methods of research, and some important facts have been brought to light. Nevertheless it must be owned that we are still ignorant as to the immediate nature of the biological processes that dispose certain subjects to the excessive accumulation of fat.

It is, of course, recognised that within certain limits the accumulation of fat is a physiological process well adapted to enable the individual to live for considerable periods of time without a supply of food adequate to the caloric expenditures. How important a part the fat depôts play in sparing proteid waste under such conditions we have already seen. The exaggeration of the conservative process of fat storage leads to the distinctly pathological state of obesity. We can draw no sharp line between the fat accumulations which are normal and those which are not. Our judgment on this point has to be formed on the condition of the individual patient, rather than on the actual quantity of fat that has been laid by. Just as soon as a fat person shows that he is distinctly less competent to perform physical and mental labour by reason of growing corpulency, he has reached the point where his fat stores are to be regarded as a menace rather than as a protection. Then it becomes necessary to institute measures for getting rid of the excessive fat. You cannot intelligently advise a patient how to do this unless you are familiar with the leading facts in the chemical pathology of corpulency. Perhaps I can make these clear to you.

It is self-evident that the fat which is laid up by the organism either to a normal or a pathological extent is derived from the food, but it is by no means obvious that the fats, the carbohydrates, and the proteids are each capable of contributing to this storage of fat. That fatty acids can be converted into neutral fat after absorption was considered incompatible with the supposition, long entertained, that syntheses are not performed by animal cells. It is now known that numerous important syntheses are carried on by animal cells, including the synthesis of fat from fatty acids and glycerin. It has also been shown that growing animals

fed on proteid and fat lay up an amount of adipose tissue that can be accounted for only on the supposition that the fatty elements of the food have been stored. Similarly, in the case of carbohydrates, it has been demonstrated that animals fed on proteids and carbohydrates gain much more fat than could possibly be derived from the proteid portion of the food. As I have already said in speaking of the carbohydrate food-stuffs, the formation of fat from sugars involves an elaborate synthesis. Of course the carbohydrate material and the fat which is stored as fat in the adipose depôts represent spare nutritive material, that is to say, material not required for the immediate caloric needs of the body. As regards the formation of fat from proteid it is much more difficult to speak with certainty. Nevertheless we know that the proteid molecule contains a carbohydrate radical, and that whenever proteid is burned a proportionate amount of carbohydrate material is liberated for combustion. In starvation the body obtains its scant supply of sugar from the breaking down of its own proteid. In bad cases of diabetes and in phlorhizin poisoning the body may get its carbohydrate material, that is to say its glucose, exclusively from the breaking down of its own proteid cell-substance. Thus the unutilised sugar, which escapes burning by the cells, finds its way into the urine in large amounts proportionate to the proteid waste. Normal cells in normal persons burn the sugar which is being split off constantly during the metabolism of proteid. But if such cells already have more than they need of carbohydrates and fats supplied by the food, why should not the carbohydrate portion of the burning proteid molecule be converted into fat and stored as such like other spare sugar? There is some reason to think that this happens whenever the body has an excess of non-nitrogenous foods.

We may therefore conclude that in health fat is formed mainly from fats and carbohydrates, and perhaps under certain conditions from the carbohydrate derivatives of the proteids of the cells. Since it is true that the formation of fat is dependent mainly on the fats and carbohydrates used as food, one would naturally expect the quantity of these food-stuffs ingested to play an important part in determining the quantity of fat that is stored. But it is also evident that there is another equally important element which enters into the question of fat storage, namely, the degree of fat

consumption. It is the relation between fat formation from fat-making food and fat consumption for the caloric needs of the body that determines whether an individual gains or loses fat. In the subject of obesity there is a disproportion between the consumption of fat and the use of fat-forming food. Let us examine a little more closely into the conditions which bring about such a disproportion.

It seems to be a well-established fact that obese persons are large consumers of food, including a liberal allowance of carbohydrates and fat. Many of them, indeed, have been addicted to gluttony. Not infrequently, too, obese people take alcohol freely, and, as I have already told you, alcohol is capable of being burned in the body and of sparing fat and probably proteid. Thus you see that the diet of the obese is one admirably adapted to the formation and storage of fat in the body. Very likely you will have no difficulty in recalling examples of obesity that have come within your own observation in which the excessive use of food was a noticeable thing. Even during infancy there may be a greatly excessive formation of fat owing to the free use of carbohydrate food such as Mellin's Food, Horlick's Malted Milk, &c. It is also likely that you can think of instances where there has been excess in the use of fat-forming food with or without alcohol, but in which the subjects failed to grow fat or were even noticeably thin. It is indeed true that there is no fixed relation between the amount of food consumed and the accumulation of fat in different individuals.

There are at least two reasons why the free or excessive use of fat-making foods is not always followed by excessive fat storage. One is that the conditions of life may be such as to occasion an unusually large consumption of fat. The other reason is to be found in the nature of the digestive processes.

You will remember that in speaking of the pathology of digestion I explained the importance of the losses in food potential that occur from excessive fermentative and putrefactive processes. I showed you that it is by no means uncommon for the carbohydrates to be decomposed to such an extent that the body receives relatively little energy from them. Proteid foods may similarly suffer excessive decomposition in the intestine. The fats undergo less important changes from decomposition, but their absorption frequently suffers in catarrhal states of the intestine. Since anything

which diminishes the quantity of nutritive material entering the blood and lymph diminishes the opportunity for fat-making, it should be clear to you that excessive fermentation and putrefaction, coupled with defective powers of absorption, are capable of interfering with the accumulation of fat. Very many persons are below the normal weight because they are robbed of the fat-making constituents of food by chronic derangements of digestion. Similarly many persons who eat to excess do not grow obese, because the caloric value of their food is distinctly reduced through chronic gastric or enteric disturbances—disturbances sometimes not sufficiently pronounced to impair the general health Thus you see that one of the requisites for obesity is a good digestion. Physicians have often made use of this fact, consciously or unconsciously, in the treatment of obesity. By resorting to measures which greatly impair the patient's power of digestion and absorption they succeed after a time in bringing about the greatly desired reduction in weight. I consider such methods of treatment indefensible.

What are the conditions that favour the combustion of fat in the body or prevent its being laid by? The most important of these is muscular exercise. I do not know whether you realise how much greater is the caloric expenditure of the body in a state of severe muscular exercise than during rest. That the difference is important is evident from the calculations of Rubner. This investigator found that the average caloric output of healthy men, averaging 70 kilos in weight, is 2,303 calories, or 32·9 calories per kilo, in a state of rest, and 3,362 calories, or 48·0 calories per kilo, during vigorous muscular exercise. The increase in caloric amounts to 45 per cent. of the expenditure in the state of rest. This fact enables us to understand how it is that an indolent person lays by nutrient material in the form of fat on a diet which would not enable him to effect this storage were he put to active work. As a matter of fact most very obese persons have lazy habits. They may not object to mental work, but they do not like to use their muscles. When such persons can be induced to take active exercise there is no difficulty in reducing the weight by drawing upon the excessive fat to meet the increased requirements, provided, of course, that the allowance of food be not increased in response to an increased appetite.

There are good reasons for the disinclination of obese

persons for exercise. Such persons become heated more quickly than normal individuals, fall readily into free perspiration, and often develop dyspnœa and other signs of cardiac fatigue.

Conditions which increase the radiation of heat from the body, and thus lead to an increased heat production, are favourable to the combustion of the stored fat, unless, indeed, the food supply be correspondingly increased. Exposure to cold is the most important of these conditions, but does not ordinarily influence the combustion of fat in the obese in an important degree. There is considerable evidence that corpulent people radiate less heat, on exposure to cold, than persons provided with an ordinary amount of fat. Thus a man weighing 83 kilos expended 76 calories in a bath of 21° to 22° C. lasting 20 minutes, whereas a normal man of 62 kilos radiated 117 calories under the same conditions. The relatively low heat production of the obese is doubtless referable in part to the protective action of the adipose layer, which is a poor conductor of heat.

It should now be clear to you that the most important factors in the treatment of obesity are the regulation of the diet and insistence on the free use of the muscles. Experience shows that there are few cases of obesity that cannot be brought within control through intelligent regulation of diet and exercise. Nevertheless it is claimed that there are obese persons whose condition is to some extent independent of over-eating and under-working. A family inclination to obesity is often noticeable, and it is thought that many of the persons with this inclination are peculiarly prone to fatten. This especial tendency to grow obese has been attributed to a slowing in the processes of metabolism, due to a diminished capacity of the cells to carry on the oxidation of fat. Let us review briefly the more important facts relating to this doctrine.

In the fasting state the respiratory gas exchange of the obese shows no deviation from the normal. Thus in three patients observed by Jacquet and Svenson the CO_2 expired per kilo averaged 2·49, 2·33, and 2·56 c.cm. per minute. The consumption of O_2 in these three cases averaged 3·29, 3·17, and 2·97 c.cm. These represent normal values. But the figures which I have just cited are based on the total cell activities of the body, inactive fat being included with the active cells of the organism. If we estimate approximately

the excess of fat in the obese individual from whom these results were obtained, and deduct this from the total weight of the body, the values for the O_2 consumed and the CO_2 expired come considerably higher. There are some minor objections to this rough method of estimating the respiratory gas exchange carried on by the active cells, but when every allowance is made for these it is clear that there is no diminution in the metabolic activity of the obese organism, and that, in some patients at least, the intensity of metabolism in the active cells is even greater than in normal persons at rest. This increased activity of metabolism is probably explained by the exaggerated activities of the respiratory muscles, which are so commonly observed in obese persons in the resting state as well as during activity

But while the obese patient shows no diminution in the intensity of metabolic combustion in the fasting condition he may react much less strongly to the influence of food than a normal individual. Thus Magnus Levy found an average augmentation of 27 per cent. in the O_2 consumption after breakfast, while Jacquet and Svenson found only an increase of 12 to 21 per cent. under similar conditions in one of their obese patients. Three hours after breakfast the increase in the consumption of O_2 still amounted to 16 per cent. in the normal subject, whereas in the corpulent person an increase was barely perceptible at this time. The influence of digestion exhibits itself normally in an increase of the CO_2 output, as well as in the greater consumption of O_2. In an obese subject the CO_2 output, like the O_2 used, is much less augmented by a meal than is normally the case The observations on the respiratory exchange of gases thus indicate that the processes of combustion in the cells are much less actively stimulated by food in persons that are obese than in normal persons. The increased combustion that normally follows the absorption of food is also of shorter duration in the subject of obesity. In other words, the over-fat individual differs from the normal in that he saves considerable food material during the period of food absorption. It has been estimated that an obese person may save 11 grams of fat per day in consequence of this diminished oxidation; that is to say, 11 grams of fat which would have been burned by a normal person under similar dietetic conditions. Such a saving as this

would account, at least in part, for the obesity of some persons. Just how this saving of food materials comes about is not yet clear. Some writers, including Speck and Zuntz and v. Mering, attribute the normal increased gas exchange following a meal to the activities of the cells of the digestive tract which are then called into play, and it has been maintained that the saving of food material in the obese is dependent on a relatively slight stimulation of the digestive glands during digestion and absorption. Serious objections to this view have been raised. Fr. Müller has pointed out the fact that there is a striking difference between the action of the carbohydrates and the proteids on the activity of combustion. Thus, while a proteid meal stimulates the intake of oxygen in a marked degree and for a prolonged period, a carbohydrate meal provokes only a slight and transient rise in the intake of oxygen; and since there is as yet no evidence that a carbohydrate meal imposes less work on the cells of the digestive tract than does a meal of proteid, we have no right to assume that the diminished combustions of obesity are due to the diminished activities of these cells. In support of this criticism is the fact that injections of sugar and peptone directly into the blood have been observed to occasion a considerable increase in the consumption of oxygen and in the production of carbon dioxide. This increase must be independent of any action of these food-stuffs upon the digestive glands.

The evidence at our disposal renders it in the highest degree probable that the increased activity in metabolism following a meal takes place after the absorption of food, and that the differences in combustive activity observed in obese and normal persons are dependent on differences in the excitability of the cells that constitute the various organs and the muscles.

Although the influence of exercise on the metabolism of the obese has not yet been sufficiently studied, the subject is one of such importance that I shall give you the results of the few observations that have been made. We are apparently justified in dividing our cases of obesity into two classes with respect to the way in which these cases react to exercise. In those instances where the corpulency is not extreme and the heart is not the seat of myocardial changes that distinctly impair its activity, the organism reacts to exercise much as in health. As in health there is an increase in the quantity

of oxygen consumed per kilo, but the amount of increase is greater in proportion to the amount of work done than is the case in lean persons. This increase in the consumption of oxygen seems to depend on the load which the corpulent individual carries : it resembles the increase which is observed when a lean person exercises with a knapsack or other load. Aside from the load in the form of fat, the obese individual does not work any less economically than a spare individual.

The case is very different where the load of flesh is so very great as to impede the movement of the patient, especially if the heart muscle be weakened through changes in the myocardial structure. Under these circumstances the work done by the patient is uneconomical, for a slight amount of exercise has the same metabolic effect on the corpulent individual that a much greater exertion has on a normal person. Thus Jacquet and Svenson speak of an obese person who consumed during active exercise a volume of oxygen which would have sufficed in a normal person for the performance of more than three times the work actually done by the corpulent individual. In the extreme degree of obesity the discomforts attending even slight exercise are so considerable that we cannot wonder at the dislike of these persons for muscular effort.

We may conclude from what I have now told you that at least some obese persons in the fasting state differ from the normal little or not at all in the activity of their metabolism. There is no evidence that in the fasting condition these people carry on oxidative processes less actively than do persons in health ; on the contrary, if we make a deduction for the presence of a mass of fat that is relatively inactive, it appears that the oxidations in other kinds of cells may be more than usually energetic. But, as we have seen, the conditions are wholly different after the ingestion of a full meal, for during digestion and absorption the corpulent individual's combustion is stimulated by food to a far less extent than is the case with ordinary people. Fat is thus spared and laid by in the body to a much larger extent than in health. The real cause of this fat-sparing process we do not know. There seems no ground to attribute it to diminished oxidative capacities of the cells. There is of course a diminished oxidation of fat, but this, like the diminished oxidation of sugar in diabetes, may be dependent on the absence of some ferment which must first lay hold of

the food-stuff before the cells can effect its oxidation. This is, however, mere conjecture.

It should be clear to you that even those corpulent persons who spare fat in the manner described are amenable to the influence of dietetic restrictions. Considering this metabolic sluggishness, there is no doubt that the quantity of food which would suffice for an ordinary man is excessive for the subject of obesity. Restrict his food in proportion to his fat-sparing powers, and he will cease to accumulate fat. We thus see that in every case of obesity, whether or not it presents congenital peculiarities of metabolism, there must be a disproportion between the food eaten and the requirements of the organism.

It may occur to you that there is a certain resemblance between diabetes and obesity. In diabetes there is under-combustion of sugar, and the unused sugar accumulates in the blood and readily escapes through the kidneys. In obesity there is under-combustion of fat, and the excessive fat, not being removable by the kidney, accumulates under the skin and elsewhere in places which are external to the cells most actively engaged in metabolic processes. In some if not in all cases of diabetes and in some cases of obesity we may reasonably suppose that the process of splitting the sugar molecule and the fat molecule respectively is impaired. There is no evidence that the cells of the body are incapable of performing oxidations normally. The sugar and fat molecules are apparently not oxidised because they have not been properly split or otherwise prepared for this oxidation. In each instance the defective and normal utilisation of nutritive material appears more or less closely connected with substances produced by specific glandular cells. The removal or disease of certain pancreatic cells is followed by diminished burning of sugar; the use of preparations of the thyroid gland is often attended by a diminution of obesity. Lastly it is by no means rare for deficient fat combustion and diminished sugar combustion to occur in the same organism. This is shown by the frequent association of diabetes with obesity, probably at least 10 per cent. of the obese being at some time subject to diabetes, while about one-third of all diabetics are corpulent.

As regards treatment you can derive your guides from what I have already said. In every case of obesity you must limit carbohydrates and fats, and if possible increase

exercise. Many of your self-indulgent and indolent patients will object to this, and your character and tact will be put to the test in the effort to get your directions obeyed. If you get little beneficial effect from the simple regulation of hygienic conditions, or if exercise seems harmful, you are justified in trying the effect of giving a preparation of the thyroid gland of the sheep.

I say you may try the effect of administering thyroid gland, for there is in fact no certainty as to the results to be obtained. This is because individuals react very differently to the preparations of the gland. Whereas some obese persons remain virtually unaffected others show a rapid diminution in weight under the use of moderate doses of the gland or its extract. This diminution in weight is not accompanied by any sense of weakness, but is on the contrary usually attended by a feeling of wellbeing. In some instances the administration of thyroid has been followed by the relief of dyspnœa. The mental hebetude and somnolence of some obese patients have also been quickly dissipated in consequence of a course of thyroid treatment.

Although numerous studies have been made of the effect of thyroid treatment upon obesity it cannot be maintained that we have a satisfactory conception of the nature of this therapeutic effect. Some facts, however, stand out clearly enough.

In the first place it is evident that in those corpulent individuals in whom thyroid treatment is most effective, the metabolic processes are greatly stimulated in consequence of the administration of the gland. You will remember that I emphasised the fact that in some obese persons there is a pronounced failure on the part of the organism to react in a normal degree to the stimulus of food ; a failure which finds expression in a consumption of oxygen and an output of carbon dioxide much below that which should occur in a state of health. Now the stimulating action of the thyroid on metabolism shows itself in the markedly increased consumption of oxygen and in the increased output of carbon dioxide that occur under the influence of a meal. The very patient who has habitually reacted only slightly to a meal rich in proteid quickly reacts to food in a wholly normal degree under the stimulating action of the thyroid gland or one of its preparations. Whether the therapeutic action of preparations of the thyroid gland is limited to such cases of

obesity as are characterised by a habitually sluggish reaction to food it is impossible to state at present, but it is reasonable to suppose that the thyroid treatment would be less efficacious in the cases of corpulency where the gas exchange is nearly normal than in those where it is much less active that normal under the influence of food.

The loss in weight that occurs during the thyroid treatment of obesity is attended with an increase in the volume of the urine. A daily increase of 500–600 c.c. in the volume of the urine has been noted even in cases where the daily intake of water has remained the same as during the period antecedent to the use of a thyroid preparation. This diuretic action of the thyroid treatment is due to the increased formation of water within the organism. The increase in the formation of water depends, of course, upon the increased combustion of fat or of carbohydrate material destined for synthesis into fat. You recall that the end-products of the combustion of fat are water and carbon dioxide. When the combustion of fat is increased, as under the influence of the thyroid gland, the increased formation of water in the cells causes an augmented flow of urine, and the increased production of carbon dioxide results in the greater expiration of carbon dioxide, to which I have already called your attention. The loss in bodily weight is nearly accounted for by the increased production and elimination of water.

A small portion of the weight lost under the influence of thyroid therapeutics is due to the loss of nitrogen from the organism. Thus a patient previously in a state of nitrogenous equilibrium may excrete 3–4 grams more nitrogen (equivalent to 6–8 grams of urea) under thyroid, the diet remaining the same. It is claimed by some observers that the increased output of nitrogen does not correspond to an increased combustion of cell proteid, but depends on the accumulation in the blood of nitrogenous products of decomposition. Without entering into a discussion of the evidence relating to this contention I may say that the observations of the best workers give strong support to the view that the increase in nitrogen output is dependent on the increased combustion of cell proteid. If we admit this to be the case it emphasises the necessity for caution in the therapeutic use of thyroid gland in corpulency, for the rapid and continued waste of cell proteid means loss of strength. A small loss of nitrogen cannot, however, be regarded as a

practical objection to the employment of thyroid extract provided we guard against a loss which impairs vigour and the sense of wellbeing.

The restriction of the use of fluids in the treatment of obesity has been extensively practised since it was originally recommended by Dancel, a French military surgeon, who noticed that the free use of fluids favoured the development of large bellies in horses. Careful observations on man have shown, however, that the influence of fluids on the accumulation of fat is small and uncertain. In some instances, indeed, the withdrawal of a considerable amount of fluid from the dietary results in a reduction of the appetite, and thus helps indirectly in the reduction of the adipose. When this effect on the appetite does not follow the restriction the loss of weight is transitory and dependent on the withdrawal of water from the blood and cells.

A moderate restriction in fluid is sometimes beneficial in corpulent individuals with weak heart action, but it is questionable if the total daily amount of fluid should ever fall below two pints.

A certain method of reducing the weight of obese persons is the persistent and free use of cathartics. By means of strong salines it is possible to prevent the absorption of food to such an extent that a rapid loss of fat is brought about. The great objection to such a method is the danger of setting up a chronic gastro-enteritis which ultimately injures nutrition and causes general debility.

The means which I have mentioned, if intelligently and insistently used, will suffice to cure your patients of obesity. It is by no means essential that your patients should go to watering places or take special cures, but it may be convenient to have them do so in some instances. Do not try to reduce the fat too rapidly—a loss of 2–4 lb a week is safer than a more rapid consumption of fat. Obese patients who have heart disease or who are extremely anæmic must be specially cared for, and it is necessary to be cautious in recommending exercise for such patients.

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